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Catalysts, Reactions, and Applications

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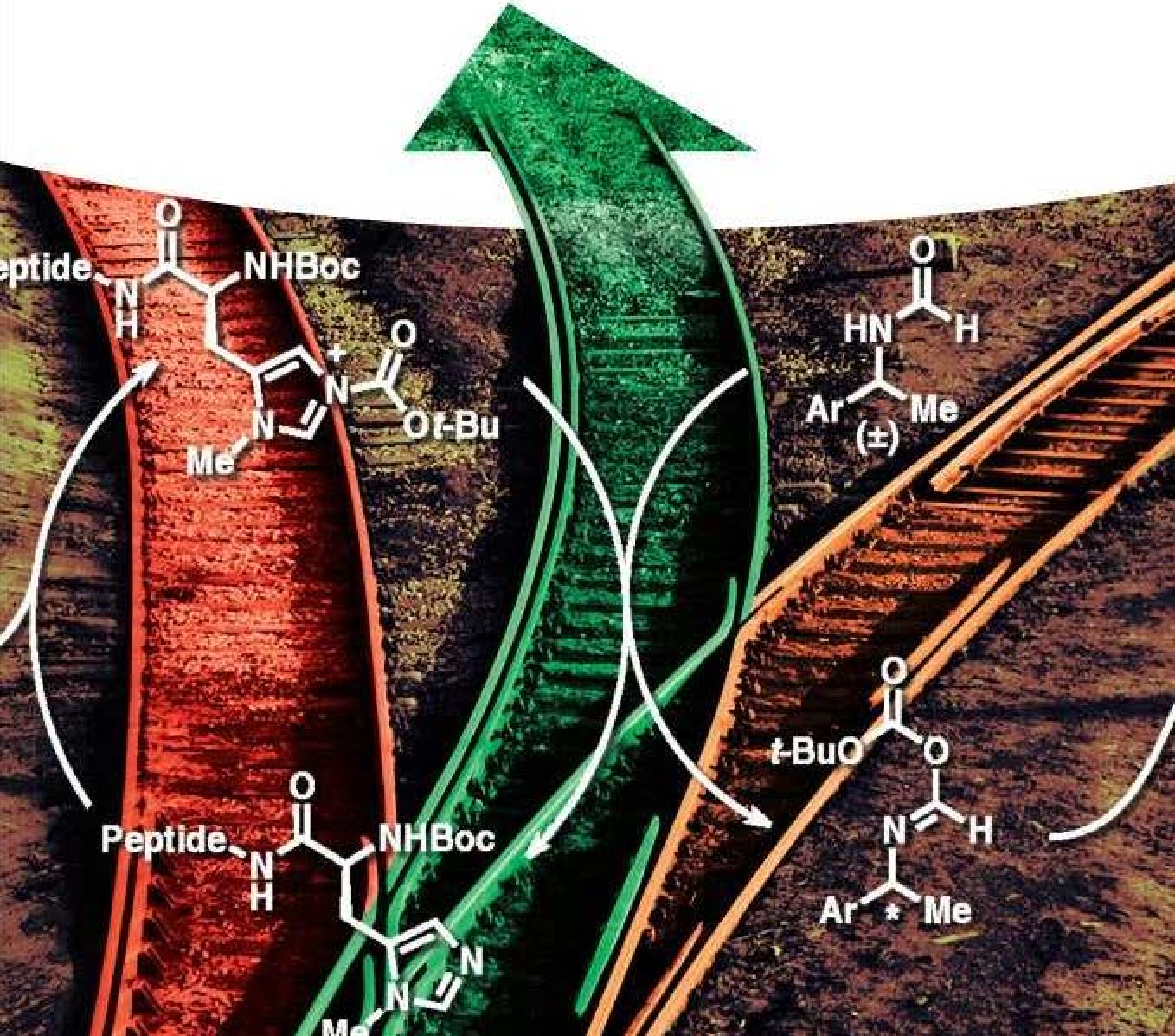

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Comprehensive Enantioselective Organocatalysis

Catalysts, Reactions, and Applications

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Comprehensive Enantioselective Organocatalysis

Catalysts, Reactions, and Applications

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Volume 3: Reactions and Applications

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Foreword

The enthusiasm and dedication with which chemists have embraced the field of organocatalysis after its inauguration in 2000 has been spectacular and somewhat resembled the quick opening of a bottle of champagne under pressure. So much catalysis needed to be rapidly discovered and revealed by an ever increasing number of researchers with so little time. First dozens, soon hundreds and later thousands of publications appeared describing the power and potential of organic catalysis. But why did all those ideas and catalysis concepts appear in such a burst? In my opinion, the organocatalysis explosion was fueled by the deeper understanding of the reactivity of organic compounds, which chemists have accumulated during the last two centuries. Without doubt, in their slow but steady advancement, organic chemists significantly benefited from the inclusion of physical methods such as kinetics, theory, and spectroscopy. The new understanding had served them very well towards the sophistication of organic synthesis, enabling chemists to make many interesting and useful molecules and materials such as drugs, dyes, polymers, and natural products. But for some reason, this understanding had hardly been applied to advancing organic catalysis. The science of catalysis had been a domain of organometallic chemistry and possibly of biochemistry but certainly not of organic chemistry. Once the first examples of rationally designed reactions catalyzed by organic molecules were disclosed though, the situation quickly became an entirely different one. All of a sudden, the accumulated knowledge of the principles of organic reactivity could immediately be applied to the design of novel catalysis concepts. For organic chemists, entering the catalysis domain by facilely illustrating that organic compounds can be active and selective catalysts very much like metals and proteins was an exciting adventure.

Now, a dozen years later, the discovery phase of organocatalysis continues relentlessly but another phase is also beginning and that is the phase of understanding and structuring organocatalysis. I think these times are equally exciting and valuable for the field. For example, many mechanistic details are still to be elucidated, including the exact nature of reactive intermediates in organocatalysis. But for me, it is also time to define the logics of organocatalysis and to give the field a certain structure. In my experience, making the effort to classify and structure an area is highly rewarding as one can easily identify uninvestigated territories, which in turn are valuable windows of opportunities for further breakthrough research.

It appears to be in this spirit that the present book is edited. I think these efforts are highly laudable and the editor has tried very hard to organize organocatalysis in a rational manner. He also has put a lot of effort on identifying the leading people in the field and on recruiting them as authors. What a massive and impressive task! Efforts such as the present one are of great value in encouraging further studies from the next generation of chemists. I hope they will be stimulated to conduct exciting new research in areas where nobody else had been before, possibly opening up another bottle . . .

Ben List

Preface

This book is the new edition of the earlier published *Enantioselective Organocatalysis* manual, which appeared six years ago. Over the past six years the organocatalysis field has progressed considerably; many new more and more powerful methods were discovered, and a new edition of this book appeared to be necessary. The aim of this multiauthor book was to recollect efficient organocatalytic reactions around clear principles that meet actual standards in asymmetric synthesis. Chapters were written in a concise way, and this condensed treatment is supported by more than 1400 schemes and figures, providing condensed visual information at a glance. The book was kept updated with the literature until spring/summer 2012. Considering the historically broad interest in the field, the book wishes to address a large audience: academic or industrial researchers, students, and teachers who are interested in synthetic organic chemistry at an advanced level.

The difficulty of discussing organocatalytic reactions in a comprehensive way lies in the dichotomy of the catalyst/reaction approach: looking at the chemistry from the catalyst side, which is usually more suitable for researchers who are developing new reactions, or discussing the topic by reaction types, which is more useful for those who wish to apply these new reactions in synthesis. The book explores a novel type of treatment by merging different approaches (catalysts, activation types, and applications), giving readers an opportunity to examine the same transformation from different points of view, allowing for some overlaps between parts. In order to give the most useful insight into this large and fast progressing field, frontline leaders who pioneered the field of organocatalysis were requested to contribute to this work. I wish to acknowledge all of the 96 authors for participating in this venture despite their already heavy responsibilities, yielding a manual of a high standard. I wish also to acknowledge the important lecture and advice of many of my colleagues and friends who assisted me in the evaluation and correction process: I am indebted to Prof. Jose L. Vicario, Prof. Helma Wennemers, Prof. Ryan Gilmour, Prof. Viresh H. Rawal, Prof. Frank Glorius, Prof. Yoshiji Takemoto, Prof. Stephen Connon, Dr. Tirayut Vilaivan, Dr. Pablo Domínguez de María, Dr. Vinod Kumar Singh, and Prof. Jieping Zhu. Also, I wish to acknowledge the help and the professionalism of Dr. Anne Brennführer and Mrs Bernadette Anna Gmeiner of STM Books, Wiley-VCH Verlag GmbH & Co.

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Abbreviations

Ac	acetyl
ACDC	asymmetric counteranion-directed catalysis
Ad	adamantyl
Ar	aryl
Alloc	allyloxycarbonyl
AQN	anthraquinone(yl)
ASD	asymmetric desymmetrization
BA	Brønsted acid
BAMOL	1,1′-biaryl-2,2′-dimethanol
BINAM	1,1′-binaphthalenyl-2,2′-diamine
BINOL	1,1′-bi-2-naphthol
Bn	benzyl (CH_2Ph)
Boc	*tert*-butoxycarbonyl
BTM	benzotetramizole
Bu	butyl
Bz	benzoyl
C	conversion
cAMP	cyclic adenosine monophosphate
CAN	cerium ammonium nitrate
cat	catalyst
CBS	Corey–Bakshi–Shibata
Cbz	benzyloxycarbonyl
CIL	chiral ionic liquid
CIP	Cahn–Ingold–Prelog
CSA	camphorsulfonic acid
Cy	cyclohexyl
DA	Diels–Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
DAG	diacylglycerol
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DCM	dichloromethane
de	diastereomeric excess
DFT	density functional theory

DBS	p-dodecylbenzenesulfonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dynamic combinatorial chemistry
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCL	dynamic combinatorial library
DEAD	diethyl azodicarboxylate
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DHIP	2,3-dihydroimidazo[1,2-α]-pyridine
DHPD	dihydrophenanthridine(yl)
DHQ	dihydroquinine(yl)
$(DHQ)_2AQN$	dihydroquinine1,4-anthraquinonediyl diether
$(DHQD)_2AQN$	dihydroquinidine1,4-anthraquinonediyl diether
$(DHQD)_2PHAL$	dihydroquinidine 1,4-phthalazinediyl diether
DIC	*N*,*N*′-diisopropylcarbodiimide
DiMePEG	poly(ethylene glycol) dimethyl ether
DIOP	2,3-(isopropylidenedioxy)-2,3-dihydroxy-l,4-bis(diphenylphosphanyl)butane)
DIPAMP	1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DIPEA	diisopropylethylamine
DKR	dynamic kinetic resolution
4-DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DTBP	di-*tert*-butyl pyridine
DUPHOS	1,2-bis(2,5-diisopropylphospholano)benzene
E	electrophile
ee	enantiomeric excess
ent	enantiomeric
er	enantiomeric ratio
Et	ethyl
ESI-MS	electrospray ionisation mass spectrometry
ET	electron transfer
EVK	ethyl vinyl ketone
EWG	electron-withdrawing group
F-C	Friedel–Crafts
FDP	fructose 1,6-diphosphate
FLP	frustrated Lewis pair
Fmoc	9-fluorenylmethyloxycarbonyl
Fu	furyl
GABA	γ-aminobutyric acid
GC	gas chromatography
HB	hydrogen bonding
HBD	hydrogen bond donating

HBTM	homobenzotetramisole
HDA	hetero-Diels–Alder
HEH	Hantzsch ester
Hex	hexyl
His	histidine
HMDS	hexamethyldisilazide
HOAT	1-hydroxy-7-azabenzotriazole
HOMO	highest occupied molecular orbital
HPEWS	Hajos–Parrish–Eder–Sauer–Wiechert
HPLC	high pressure liquid chromatography
HQ	hydroquinone
HSBM	high speed ball milling
HWE	Horner–Wadsworth–Emmons
Hyp	4-hydroxyproline
β-ICD	β-isocupreidine
IL	ionic liquid
IMDA	intramolecular Diels–Alder
IP	ionization potential
IP3/DAG	inositol triphosphate/diacylglycerol pathway
ISC	intersystem crossing
KIE	kinetic isotopic effect
KR	kinetic resolution
LB	Lewis base
Leu	leucine
LUMO	lowest unoccupied molecular orbital
MAOS	microwave-assisted organic synthesis
MAPK	mitogen-activated protein kinase
MCA	methyl cation affinity
MBH	Morita–Baylis–Hillman
MCR	multicomponent reaction
Me	methyl
MINECO	Ministry of Economy and Competitivity
MM	molecular modeling
MO	molecular orbital
MOE	Ministry of Education
MLCT	metal-to-ligand charge transfer
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
MW	microwave
N/A	not available
Naph	naphthyl
NBA	*p*-nitrobenzoic acid
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide

NHC	*N*-heterocyclic carbene
NMI	*N*-methylimidazole
NMP	nitroxide-mediated polymerization
NMR	nuclear magnetic resonance
Nu	nucleophile
PA	proton affinity
PBO	*P*-aryl-2-phosphabicyclo[3.3.0]octane
PCC	pyridiniumchlorochromate
PEG	polyethylene glycol
PEG-PS	poly(ethylene glycol)-polysytyrene
Pent	pentyl
PG	protecting group
Ph	phenyl
PHAL	phthalazine(yl)
PHANOL	paracyclophanediol
Phe	(*S*)-phenylalanyl
PINDOX	bipyridine mono-*N*-oxide
PIP	2-phenyl-2,3-dihydroimidazo[1,2a]pyridine
PIQ	2-phenyl-1,2-dihydroimidazo[1,2a]quinoline
PKR	parallel kinetic resolution
PMB	*para*-methoxybenzyl
PMBA	*para*-methoxybenzoic anhydride
PMP	*para*-methoxyphenyl
POM	polyoxometalate
POSS	polyhedral oligomeric silsesquioxanes
4-PPY	4-(pyrrolidino)pyridine
Pr	propyl
PS	polystyrene
PTC	phase transfer catalyst
PTC	phase transfer condition
pTSA	p-toluenesulfonic
PVC	polyvinyl chloride
PYDZ	pyridazine(yl)
PYR	pyrimidine(yl) or pyrazolidine(yl)
*o*QDMS	*ortho*-quinodimethanes
QDN	quinidine-1-naphthoate
RAFT	reversible addition-fragmentation chain transfer
R-CSA	(*R*)-camphorsulfonic acid
R-Phe	(*R*)-phenylalanine
RDS	rate-determining step
*rec*SM	recovered starting material
RNA	ribonucleic acid
rt	room temperature
RTIL	room temperature ionic liquids
s	selectivity factor

SCE	saturated calomel electrode
sec	secondary
SET	single electron transfer
SOMO	self-occupied molecular orbital
TA	thiourea-amine
TBSO	*tert*-butyldimethylsilyl ether
TADDOL	α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TADMAP	3-(2,2,-triphenyl-1-acetoxyethyl)-4-dimethylamino)pyridine
TBAP	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFFA	trifluoroacetic acid
TFE	trifluoroethanol
TfOH	trifluoromethanesulfonic acid
TFPB	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Thr	threonine
THT	thiolane
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TOF	time of flight (for the mass spectrometry technique)
Tol	tolyl
TPFPB	tetrakis(pentafluorophenyl)borate
Trt	trityl (triphenylmethyl)
Ts	4-toluenesulfonyl (tosyl)
TS	transition state
TSA	transition state analog
UNCA	urethane-protected α-amino acid *N*-carboxy anhydride
VANOL	3,3′-diphenyl-2,2′-bi-1-naphthol
VAPOL	2,2′-diphenyl-(4-biphenanthrol)
W/O	water/oil

Part I
Amino Acid-Derived Catalysts

1

Proline-Related Secondary Amine Catalysts and Applications

Hiyoshizo Kotsuki and Niiha Sasakura

1.1

Introduction

Since the reappearance of L-proline (**1**) at the forefront of organocatalysis, tremendous efforts have been made to devise new catalysts based on a proline core structure. In this field, the chirality of a pyrrolidine fragment plays a critical role, and the principal concept that underlies the development of new catalysts can be simply explained as the attachment of acidic sites in place of a carboxylic acid group to the side chain. Accordingly, several catalysts with various acidic functionalities have been developed [1]. In general, proline-based organocatalysts can be classified into six major categories: (A) prolinamides, (B) prolinamines, (C) proline tetrazoles, (D) prolinamine sulfonamides, (E) prolinamine thioureas, and (F) diarylprolinols (Figure 1.1). Representative pK_a values of these catalysts are listed in Figure 1.2 [2]. A subtle change in the side-chain assembly may change the pK_a value in the range 8–20, which would have a significant effect on the strength of hydrogen bonding, and thus the catalytic activity and selectivity may be affected.

In this chapter we will deal with organocatalytic asymmetric transformations using these catalysts, mainly focusing on the significant and major achievements in this area published from 2000 to 2011. However, due to space constraints, this chapter will not cover the great utility of diarylprolinol catalysts (category F); for convenience, only references are given [3].

1.2

Prolinamide and Related Catalysts

Owing to the ready availability of prolinamide derivatives through the condensation of proline with amines, prolinamide-based compounds constitute a large family of organocatalysts [4]. Figure 1.3 lists representative examples of these catalysts.

Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, First Edition.
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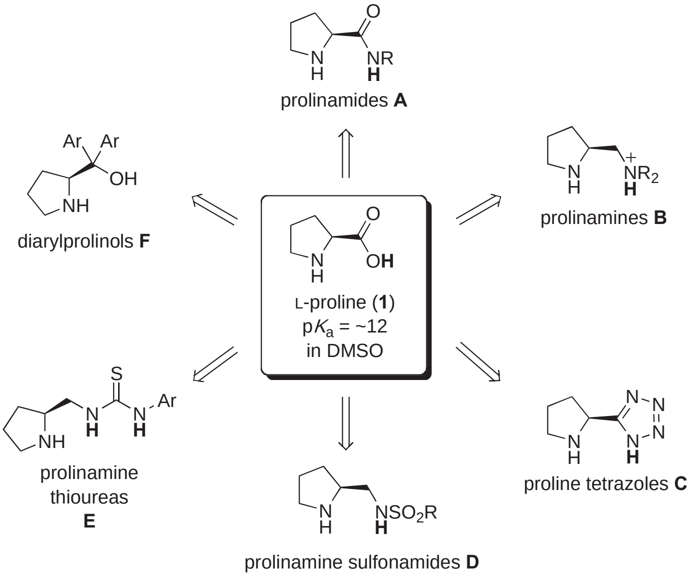


Figure 1.1 Major classes of proline-based organocatalysts.

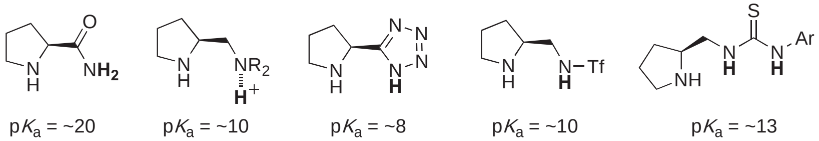


Figure 1.2 pK_a values of representative proline-related compounds (in DMSO).

These catalysts are very useful in a wide range of asymmetric syntheses. Asymmetric aldol reactions have been investigated by several research groups; selected examples are compiled in Scheme 1.1.

In this context, prolinamide **2** [5–8] and its aryl-substituted homologs such as **3**–**5** have been developed [9–14]. Analogous to these examples, binaphthyldiamine-derived compounds such as **6** and **7** have been introduced for use in aqueous systems and as recoverable catalysts [15–18]. For example, Benaglia and coworkers reported that the prolinamide catalyst **7** with a lipophilic side chain showed efficient catalytic activity in water [16b]. Chiral spiro diamine-derived catalysts have also been designed, albeit in moderate enantioselectivity [19]. Owing to the increased acidity of an NH group of thioamide relative to a normal amide, proline-thioamide catalysts such as **8** have been shown to be more effective [20–23].

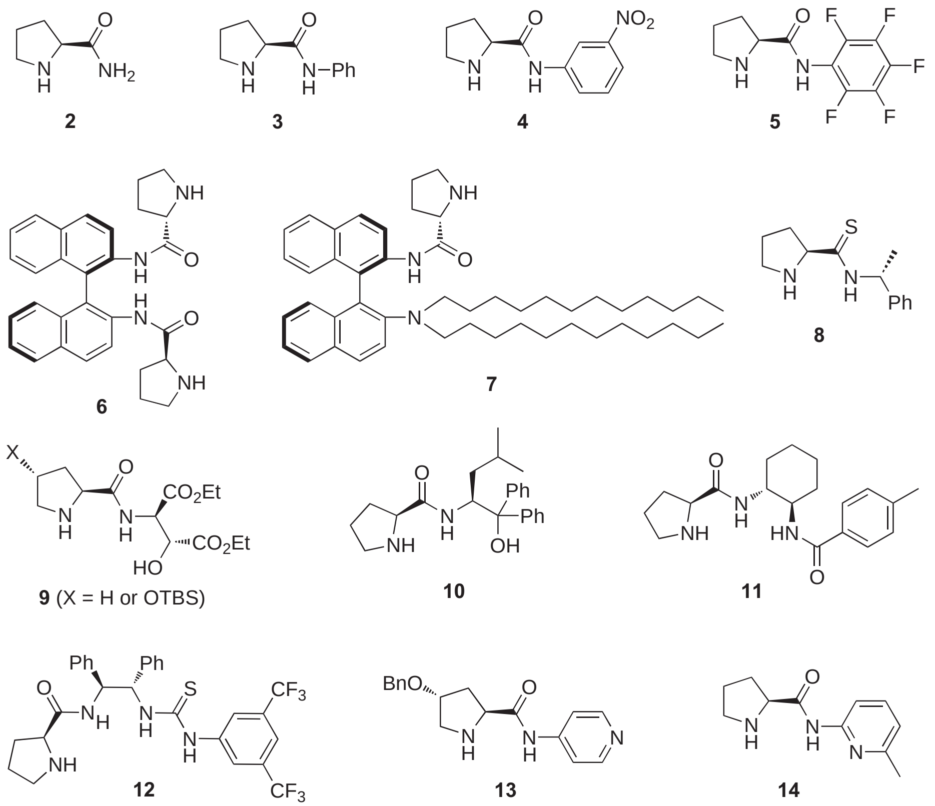
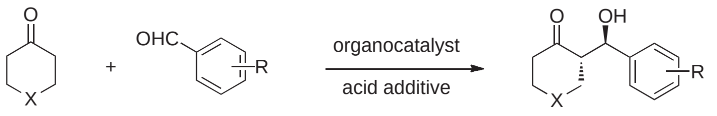


Figure 1.3 Representative examples of prolinamide organocatalysts.



cat **4** [Ref 9d]
yield: 86-92%
de: 60-92%
ee: 88-96%

cat **5** [Ref 13]
yield: 42-90%
de: 92-98%
ee: 90-98%

cat **6** [Ref 15a]
yield: 98-99%
dr: 4.3 : 1 to 10 : 1
ee: 90-93%

cat **7** [Ref 16b]
yield: 35-100%
de: 80-98%
ee: 53-93%

cat **9** [Ref 24h]
yield: 50-99%
de: 92-98%
ee: 92-98%

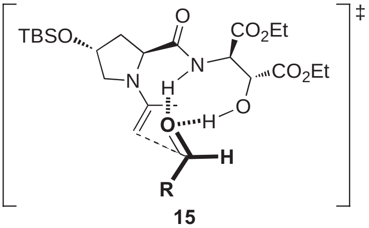
cat **10** [Ref 26b]
yield: 69-85%
de: 72-98%
ee: 83-99%

cat **11** [Ref 43a]
yield: 41-94%
de: 60-98%
ee:77-97%

cat **12** [Ref 48]
yield: 61-100%
de: 86-96%
ee: 88-99%

Scheme 1.1

A successful approach in this field is the design of multifunctionalized catalysts such as **9** and **10** through the incorporation of chiral aminoalcohol and related species onto the side chain [24–35]. The high catalytic activity and enantioselectivity of catalyst **9** can be explained by considering the favorable assembly of donor and acceptor molecules via double hydrogen-bonding stabilization, as depicted in the transition state model **15** [24h]. In these examples, to gain satisfactory results, it is important to match the chirality between the proline core and the attachment.



15

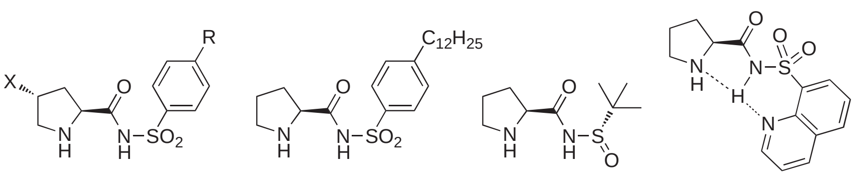
Several other related systems containing a prolinamide or proline-thioamide core have also been reported [36–42].

In some cases, a chiral diamine assembly can serve as an effective scaffold for the design of multiply functionalized catalysts like **11** and **12** [43–49]. Proline hydrazides [50], dipeptides [51–57], or other small peptides [58–63] bearing a prolinamide core have been shown to be useful in asymmetric aldol reactions.

Catalyst **13** was introduced for use in aqueous systems in the presence of surfactant Brønsted acids as co-catalysts [64], and several other catalysts such as **14** containing a heteroaromatic system have also been reported [65–67].

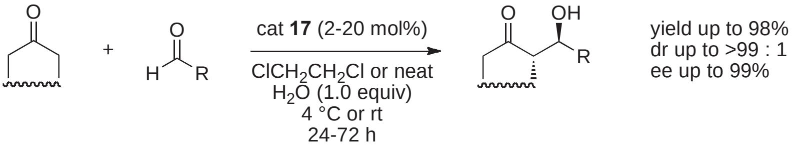
There has been important progress in the use of proline sulfonamides (pK_a = 8–11) [2] as efficient organocatalysts, and Yang and Carter provided an excellent review [68]. Therefore, only a few important aspects are addressed here. Figure 1.4 lists representative examples of these catalysts.

Various *N*-arylsulfonyl-substituted prolinamides such as **16** have been used in asymmetric aldol reactions [69–78]. Carter and coworkers actively sought new efficient catalysts of this type, and found that **17** could serve as an efficient catalyst for asymmetric aldol reactions, even in the absence of any organic solvent, with excellent diastereo- and enantioselectivity (Scheme 1.2) [79].



16 **17** **18** **19**

Figure 1.4 Representative examples of proline sulfonamide organocatalysts.

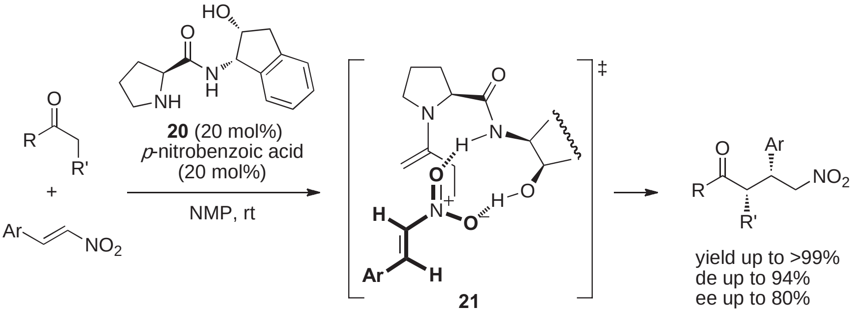


Scheme 1.2

Recently, Ellman and coworkers have shown that chiral sulfinate **18** can catalyze asymmetric aldol reactions of acetone, whereas proline (**1**) itself gave poor results [80]. Nakamura and coworkers also explored this field, and found that **19** can promote the asymmetric cross-aldol reaction of acetone with activated ketones, to generate a quaternary carbon stereogenic center bearing an OH function [81].

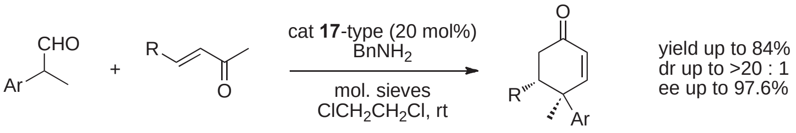
With regard to aldol chemistry, Mannich or domino-Mannich–Michael reactions can also be promoted by *N*-arylsulfonyl-substituted prolinamide catalysts such as **17** with high levels of enantioselectivity [82, 83].

Importantly, prolinamide catalysts work well in Michael addition reactions using nitroolefins as acceptors [58, 64, 84–95]. For example, Nájera and coworkers used bifunctional catalyst **20** by virtue of the synergistic effect of double hydrogen-bonding activation, as depicted in the transition state model **21** (Scheme 1.3) [90]. For the same purpose, prolinamides containing a heteroaromatic system like **14** have also been reported [96].



Scheme 1.3

Analogously to these examples, proline-derived peptide catalysts can also efficiently promote Michael addition reactions [97–99]. Prolinamide or prolyl sulfonamide catalysts are also effective for intramolecular Michael addition reactions [100–102]. Recently, Yang and Carter reported a short-cut strategy to construct an all-carbon substituted quaternary carbon stereogenic center on a cyclohexenone framework via Robinson-type annulation using the **17**-type catalyst (Scheme 1.4) [103].



Scheme 1.4

While some examples of prolinamide-catalyzed enantioselective Biginelli condensation [104, 105] and other types of C–C bond formation [106, 107] are known, their synthetic utility is unclear. Finally, for convenience, with regard to asymmetric heteroatom functionalization and transfer hydrogenation using prolinamides as catalysts, only references are given [108–114].

1.3
Prolinamine and Related Catalysts

Among several organocatalysts derived from L-proline (**1**) as a chiral source, pyrrolidine–tertiary amine conjugates constitute a powerful and useful family in asymmetric synthesis [115]. In 1994, Kawara and Taguchi reported pioneering work on the use of such catalysts in asymmetric Michael addition reactions [116]. Since then, several related catalysts have been developed. Figure 1.5 lists representative examples.

In 2001, after screening several chiral diamines and protonic acid additives, Yamamoto and coworkers reported that a TfOH salt of **22** could efficiently promote asymmetric aldol reactions [117]. Thereafter, similar studies using chiral diamines such as **22–24** with Brønsted or Lewis acid additives have also been reported [118–122]. In 2006, the Mase/Takabe/Barbas groups discovered that prolinamine catalyst **25** with a lipophilic side chain showed efficient catalytic activity in water (Scheme 1.5) [123]. Thus, cyclohexanone reacts smoothly with various aldehydes in water to afford the desired aldol products in high yields with excellent diastereo-

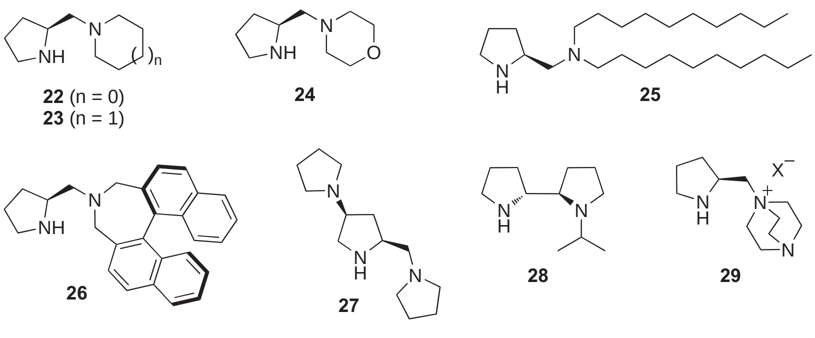
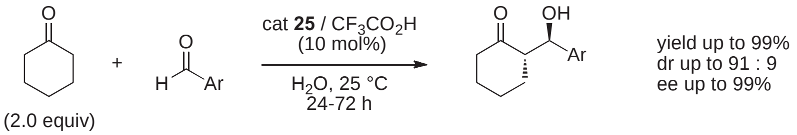


Figure 1.5 Representative examples of prolinamine organocatalysts.

and enantioselectivity. Recently, the recyclability of analogous catalysts has been reported by others [124].

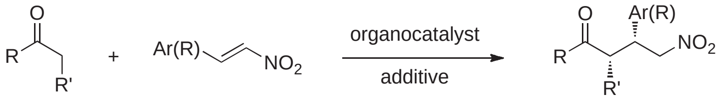


Scheme 1.5

Prolinamine catalyst **26** has been introduced for the same purpose [125].

With regard to asymmetric aldol reactions, it has been shown that prolinamine catalysts such as **22** can also work well for intramolecular aldol [126–128], Henry (nitroaldol) [129], Mannich [130, 131], and domino-Michael–aldol reactions [132] as valuable asymmetric transformations.

Similar to aldol chemistry, prolinamine-catalyzed asymmetric Michael addition reactions have attracted considerable attention from synthetic chemists, and successful examples have been developed (Scheme 1.6).



cat **22** [Ref 133c]
additive: CF_3CO_2H
in *i*-PrOH, at 4 °C
yield up to 96%
dr up to *syn/anti* = 89 : 11
ee up to 91%

cat **24** [Ref 133b]
additive: no
in THF, at rt
yield up to 96%
dr up to *syn/anti* = 98 : 2
ee up to 78%

cat **25** [Ref 140]
additive: CF_3CO_2H
in brine, at 25 °C
yield up to 99%
dr up to *syn/anti* = 98 : 2
ee up to 97%

cat **26** [Ref 141]
additive: CF_3CO_2H
in brine, at rt
yield up to 98%
dr up to *syn/anti* = 99 : 1
ee up to 99%

cat **27** [Ref 138]
additive: Tf_2NH
in *i*-PrOH, at 0 °C
yield up to 99%
dr up to *syn/anti* = 99 : 1
ee up to 98%

cat **28** [Ref 143a]
additive: HCl or *p*-TsOH
in $CHCl_3$, at rt or 60 °C
yield up to 99%
dr up to *syn/anti* = 96 : 4
ee up to 85%

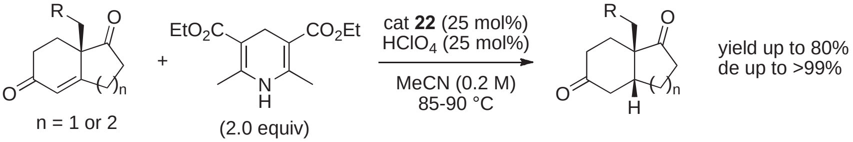
Scheme 1.6

In this field, prolinamine catalysts **22** and **24** are particularly useful for promoting asymmetric Michael addition reactions between several donor and acceptor molecules [120b, 133–136]. On a related topic, catalyst **27** and related diamine or triamine catalysts have been developed [137–139]. Interestingly, the Mase/Takabe/Barbas groups reported that diamine catalyst **25** could again serve as an efficient catalyst for asymmetric Michael addition reactions even in brine solution [140]. Similarly, several types of water-active catalysts such as **26** have been developed [141, 142].

Independently, Alexakis and coworkers reported that 2,2′-bipyrrolidine catalyst **28** showed excellent catalytic activity in several types of asymmetric Michael addition reactions [143]. It has been postulated that the isopropyl group on one of the C_2-symmetric pyrrolidine rings should block not only the back face against the approach of Michael acceptors but also shift the equilibrium towards one of the two rotamers. Since then, closely related catalysts have also been reported [144]. Furthermore, different types of catalysts such as **29** have been shown to be useful in asymmetric Michael addition reactions [145–148].

While catalyst **22**/**23** has been known to be valuable in other C–C bond-forming strategies, for example, 1,3-dipolar cycloaddition [149], hetero-Diels–Alder reaction [150], Friedel–Crafts-type alkylation [151], double-Michael reaction [152], [2,3]-Wittig rearrangement [153], and Claisen–Schmidt condensation [154], only references are given here.

Finally, while various reactions under the catalysis of **22** or **24**, for example, asymmetric epoxidation of α,β-unsaturated aldehydes [155], β-hydroalkoxylation of α,β-unsaturated enones [156], and stereoselective reduction of α,β-unsaturated enones (Scheme 1.7) [157], have also been reported, they have been demonstrated in only a limited number of experiments.

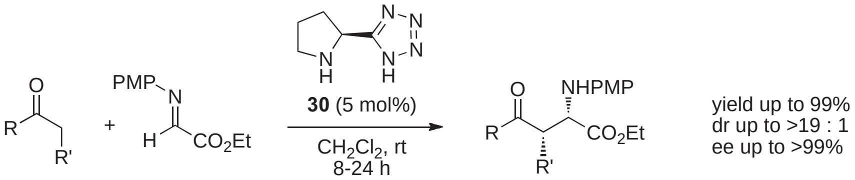


Scheme 1.7

1.4
Proline Tetrazole and Related Catalysts

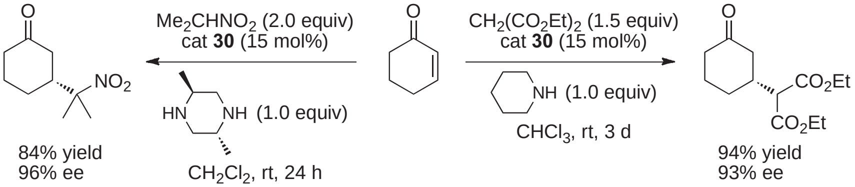
Proline tetrazole catalysts (category C in Figure 1.1) are readily accessible from L-proline (**1**) [158]. They are remarkably useful in asymmetric synthesis [159]. As shown in Figure 1.2, the pK_a of tetrazole is very similar to that of carboxylic acid. Moreover, the advantage of tetrazole catalysts is their robust and lipophilic nature compared to L-proline (**1**) itself, which allows them to escape parasitic bicyclo-oxazolidinone formation [160].

In 2004, Yamamoto and Arvidsson independently reported the catalytic activity of the L-proline tetrazole catalyst **30** in asymmetric aldol reactions of ketones with aldehydes [161–163]. At the same time, Ley and coworkers reached similar conclusions by applying this system to asymmetric Mannich and Michael addition reactions (Scheme 1.8) [164]. Since then, the scope of this chemistry has been expanded by several research groups [165–174].



Scheme 1.8

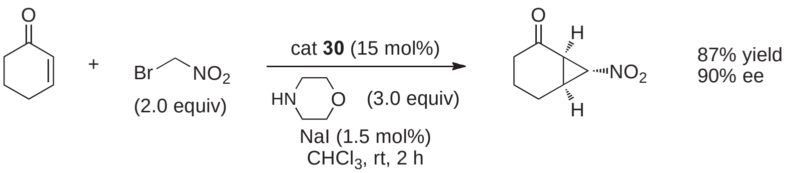
Ley and coworkers have been quite active in this field, and have found that **30** or its homolog could efficiently promote asymmetric Michael addition reactions using various Michael acceptors and donors [164b, 175]. In these cases, the reactions require the use of a basic amine such as *trans*-4,5-dimethylpiperazine as a co-catalyst to increase the nucleophilicity of donor molecules by deprotonation. Typical examples are shown in Scheme 1.9.



Scheme 1.9

A mechanistic investigation of this chemistry using density functional theory calculations [176] and reactions in ionic liquids as solvents have also been reported [177].

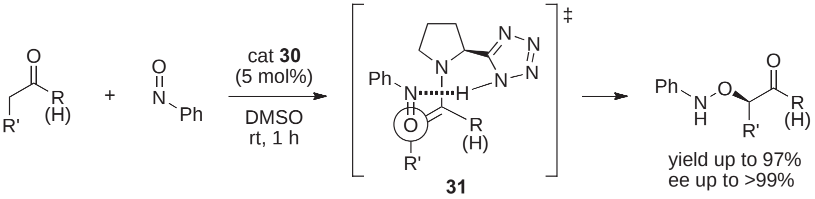
Interestingly, the Michael addition reaction of bromonitromethane to cyclic or acyclic enones constitutes a convenient way of preparing cyclopropane ring compounds in moderate to good enantioselectivity (Scheme 1.10) [178].



Scheme 1.10

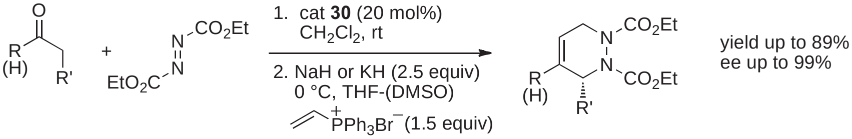
Very similar results have also been reported with the use of sulfur ylides as donor molecules [179]. With regard to the asymmetric Biginelli reaction [180] and multicomponent coupling reactions [181] using **30** or its analog as a catalyst, only references are given here.

Finally, we should emphasize the synthetic utility of the **30**-catalyzed α-oxidation of carbonyl compounds via an "*O*-nitroso aldol reaction" [182]. This method is very attractive as a metal-free oxidation system. For example, Yamamoto and coworkers found that aminoxylation reactions of ketones or aldehydes proceed with almost perfect enantioselectivities (97–99% ee) in the presence of **30** as a catalyst (Scheme 1.11) [183]. Mechanistically, nitroso compounds possess two electrophilic centers, that is, nitrogen and oxygen atoms, but the exclusive formation of O-alkylation products indicates that a hydrogen-bonding transition state like **31** seems to be satisfactorily stabilized with the more basic nitrogen atom. As an extension of this strategy, asymmetric domino-Michael–aldol reactions have also been developed by these authors, and these provide a convenient way to prepare 3-oxa-2-aza-bicycloketone derivatives in high enantioselectivity [184].

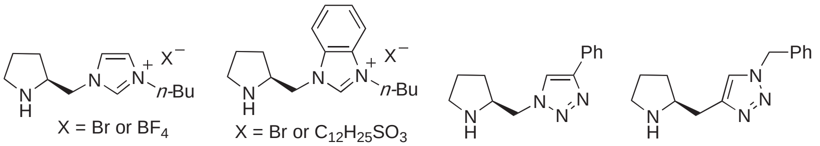


Scheme 1.11

Since then, extensive efforts have been made to apply this method to other multiple functionalizations [185–189] or to discover other possible oxidizing agents such as *N*-sulfonyloxaziridines [190]. As a related chemistry, asymmetric amination at the α-position of a carbonyl compound has also been reported with the use of azodicarboxylate esters as electrophiles [187c, 191–194]. Ley and coworkers have developed an ingenious strategy for obtaining chiral dihydropyridazine derivatives by the combination of asymmetric α-amination and Wittig olefination in a one-pot operation (Scheme 1.12) [187c, 192a].



Scheme 1.12



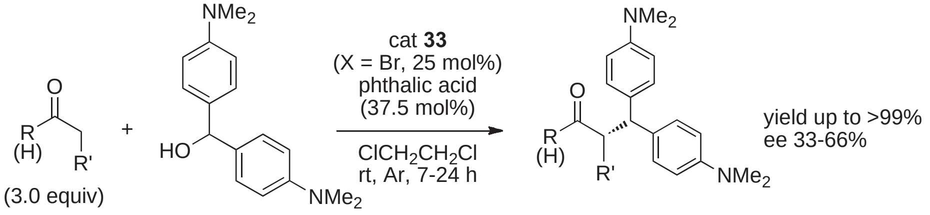
32 **33** **34** **35**

Figure 1.6 Representative examples of proline-based heterocyclic organocatalysts.

As a different family of heteroaromatic-substituted organocatalysts, imidazole- and triazole-based compounds have been known to be quite effective for asymmetric aldol and Michael addition reactions. Figure 1.6 lists representative examples of these catalysts.

The utility of ionic liquid conjugate catalysts such as **32** and **33** can be ascribed to their recyclability [195–199]. On the other hand, triazole-based catalysts such as **34** and **35** are readily accessible via Huisgen 1,3-dipolar cycloadditions, so-called "click reactions," from azidomethyl-pyrrolidine and acetylenic precursors, and hence make it possible to design new immobilized catalysts [200–207].

Interestingly, it has been shown that the **33**-catalyzed asymmetric S_N1-type α-alkylation of aldehydes or ketones proceeds well in excellent diastereoselectivity and good enantioselectivity (Scheme 1.13) [208].

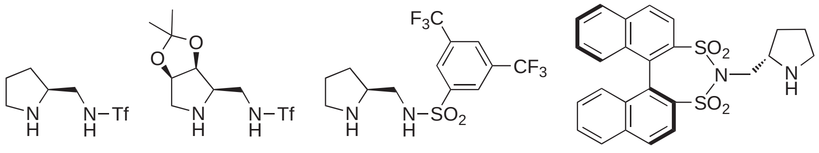


Scheme 1.13

1.5
Prolinamine Sulfonamide and Related Catalysts

Prolinamine sulfonamide catalysts (category D in Figure 1.1) can be envisaged as a reversal of prolinamides (A), and constitute a fascinating group of organocatalysts. The catalytic activity of these compounds can be ascribed simply to the sufficient acidity ($pK_a = 10$) of a sulfonamide key structure (Figure 1.2). Figure 1.7 lists representative examples of these catalysts.

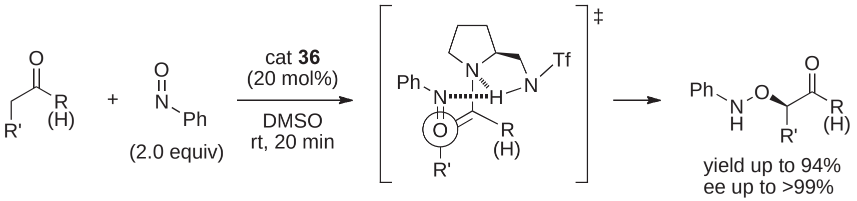
For example, in 2004, Wang and coworkers reported a series of asymmetric transformations, for example, α-aminoxylation, Mannich reactions, and α-sulfenylation, under the catalysis of pyrrolidine trifluoromethanesulfonamide **36**; the product yields and diastereo- and enantioselectivities are quite good in most



36 **37** **38** **39**

Figure 1.7 Further representative examples of prolinamine sulfonamide organocatalysts.

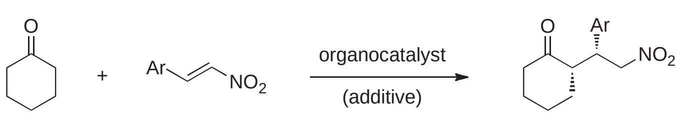
cases [209–211]. The proposed mechanism is essentially the same as that in the case of tetrazole catalyst **30** (Scheme 1.14); in contrast to the planar nature of a tetrazole in **30**, a trifluoromethanesulfonyl group in **36** is non-planar. This difference may change the stability of a hydrogen-bonding network at the transition state.



yield up to 94%
ee up to >99%

Scheme 1.14

After these reports, the same group extended the utility of this catalytic system to asymmetric Michael addition and aldol reactions [212, 213]. Sulfonamide catalysts such as **37–39** have also been developed for the same purpose [214–219]. The behavior of these catalysts, typically exemplified by enantioselective Michael addition reactions of cyclohexanone with nitroolefins, is compiled in Scheme 1.15.



cat **37** [Ref 212d]
in *i*-PrOH, at 0 °C
yield up to 96%
dr up to *syn/anti* = 50 : 1
ee up to 99%

cat **38** [Ref 216b]
in *i*-PrOH, at rt
yield up to 93%
dr up to *syn/anti* = 99 : 1
ee up to 99%

cat **39** [Ref 219a]
additive: $PhCO_2H$ (10 mol%)
in CH_2Cl_2 at 0 °C
yield up to 97%
dr up to *syn/anti* = >99 : 1
ee up to 96%

Scheme 1.15

With regard to the asymmetric α-amination of carbonyl compounds using pyrrolidine sulfonamides as catalysts, only references are given here [220, 221].

1.6
Prolinamine Thiourea and Related Catalysts

Prolinamine thiourea catalysts (category E, Figure 1.1) have been introduced primarily for the purpose of designing new bifunctional catalysts by connecting a pyrrolidine base with a remote hydrogen-bonding thiourea function [222]. Figure 1.8 lists representative examples of these catalysts.

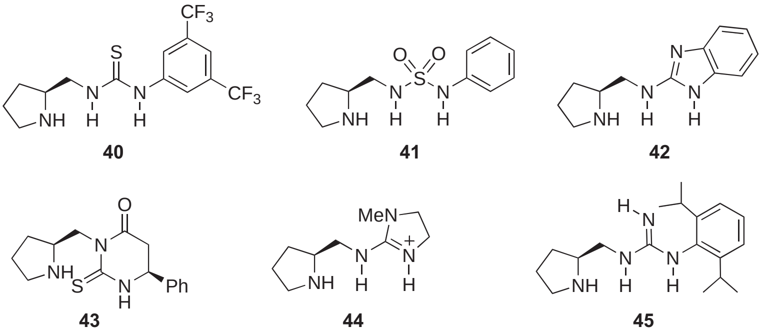
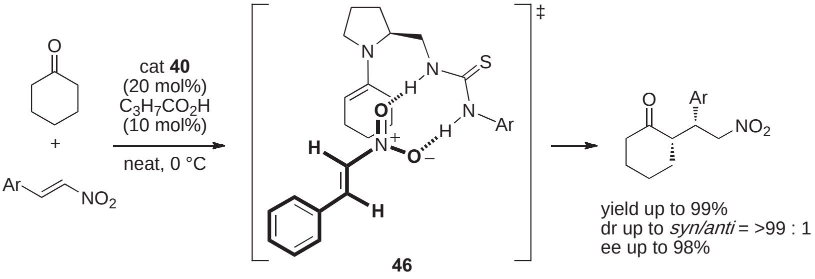


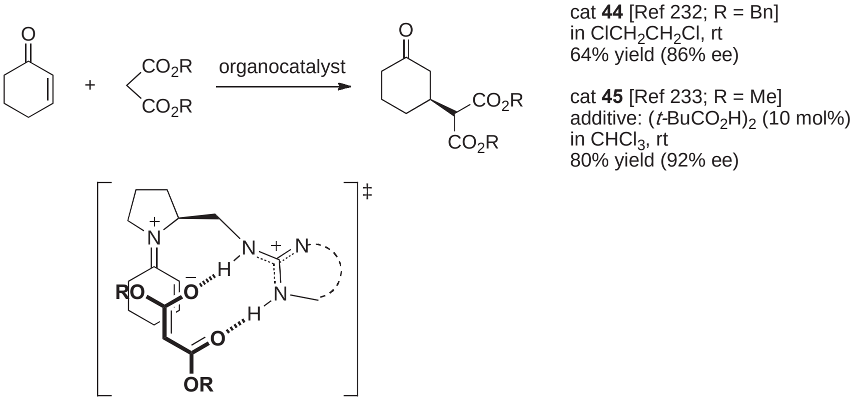
Figure 1.8 Representative examples of prolinamine thiourea conjugates and related organocatalysts.

For example, Tang and coworkers found that bifunctional thiourea catalyst **40** could efficiently promote the asymmetric Michael addition reactions of ketones or α-branched aldehydes with various Michael acceptors (Scheme 1.16) [223]. In particular, the driving force in the present system can be ascribed to the strong hydrogen bond-forming character of thiourea with nitroolefin acceptors, as depicted in the transition state model **46.**



Scheme 1.16

Since then, extensive efforts have been made to devise new powerful catalysts such as **41**–**43** through the modification of a key element of **40**, albeit in most cases with similar or less efficiency [224–231]. Guanidinyl catalysts such as **44** and **45** have been developed to realize the conjugate addition reaction of malonates or nitroalkanes to α,β-unsaturated enones in high enantioselectivity, although the number of experiments has been limited (Scheme 1.17) [232, 233]. A plausible mechanism to account for the (*S*)-configuration of the major products can be ascribed to the transition state model **47**.



cat **44** [Ref 232; R = Bn]
in $ClCH_2CH_2Cl$, rt
64% yield (86% ee)

cat **45** [Ref 233; R = Me]
additive: (t-$BuCO_2H)_2$ (10 mol%)
in $CHCl_3$, rt
80% yield (92% ee)

47

Scheme 1.17

Finally, it has been shown that thiourea-type bifunctional catalysts are also useful for asymmetric aldol reactions [234, 235] and α-chlorination of aldehydes [236]. Furthermore, 4-substituted bifunctional analogs have been developed for use in *anti*-selective Mannich reactions [237].

1.7
Miscellaneous

As described so far, various pyrrolidine-based chiral organocatalysts open the door to a remarkably fruitful world of synthetic chemistry. In general, the synthetic protocol used to design new catalysts relies on the naturally occurring chiral source L-proline (**1**) as a key component. This should be a reasonable approach to achieving final success by mimicking "nature." To characterize newly designed organocatalysts, carbonyl group functionalization, typically through Michael addition and aldol reactions, seems to be the easiest and most useful approach. These transformations are initially driven by the condensation of carbonyl compounds with a

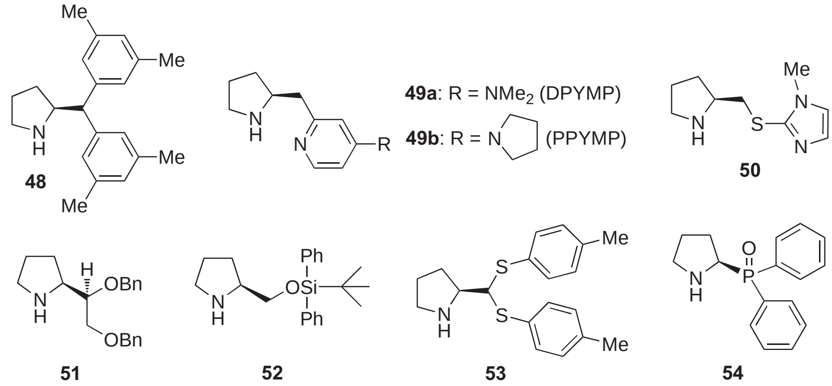
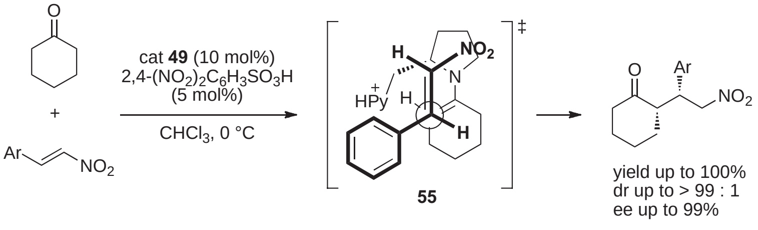


Figure 1.9 Various types of proline-related organocatalysts.

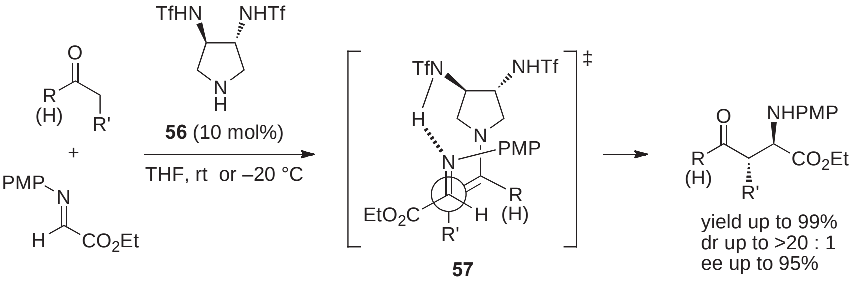
chiral pyrrolidine secondary amine to reversibly form iminium-enamine intermediates, but relatively low enantioselectivities were observed in aldol reactions catalyzed by proline ester congeners [238], except in the case of Loh's catalysts [239]. Hence, several different types of proline-related organocatalysts have been developed. Figure 1.9 lists representative examples of these catalysts.

For example, in 2003, Melchiorre and Jørgensen reported that the enantioselective Michael addition reaction of aldehydes with vinyl ketones proceeded efficiently in the presence of **48** as a catalyst (yield up to 93%, ee up to 85%) [240]. In our research laboratory, we have also been very interested in devising new catalysts with a pyridine ring as a rigid planar base adjacent to a pyrrolidine chiral ring. Along these lines, a series of new catalysts (**49**), that is, DPYMP [49a] and PPYMP [49b], were prepared from L-prolinol, and we found that they showed excellent catalytic activity in terms of productivity, diastereoselectivity, and enantioselectivity (Scheme 1.18) [241]. The results can be explained by invoking the transition state model **55**, in which the pyridinium ring must effectively shield the *Si*-face of an enamine double bond.



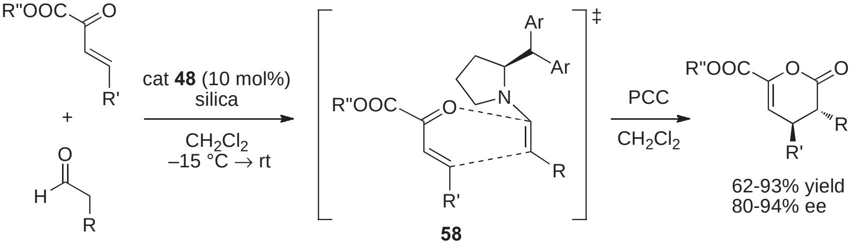
Scheme 1.18

For the same purpose, various chiral pyrrolidine catalysts such as **50–54** have also been introduced [242–250]. The versatile nature of pyrrolidine catalysts has been recognized by other transformations: aldol reaction [251], Mannich-type reaction [252, 253], and oxa-Michael reaction [254]. Among these, Maruoka's work on *anti*-selective Mannich reactions is noteworthy (Scheme 1.19, compare with Scheme 1.8) [253]. In this case, the remote hydrogen-bonding form **57** derived from catalyst **56** can overcome the steric preference so that the opposite sense of stereochemistry should be observed.



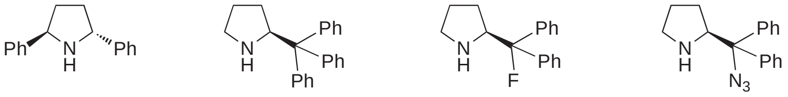
Scheme 1.19

In 2003, Juhl and Jørgensen found that, after screening a series of pyrrolidine catalysts, catalyst **48** is again of great value for the inverse-electron-demand hetero-Diels–Alder reaction: after pyridinium chlorochromate (PCC) oxidation, lactone products could be obtained as a single diastereomer in excellent enantioselectivity (Scheme 1.20) [255]. The proposed transition state model **58** indicates effective shielding of the *Si*-face of the enamine double bond by the diarylmethyl substituent on the pyrrolidine ring of the catalyst.



Scheme 1.20

A closely related study has also been reported with the use of a **53**-type catalyst [256].

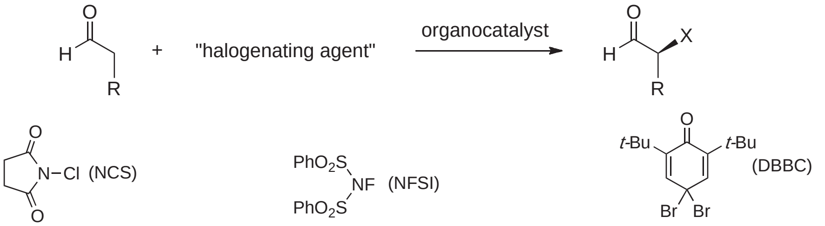


59 **60** **61** **62**

Figure 1.10 Miscellaneous examples of pyrrolidine-based organocatalysts.

Finally, another set of pyrrolidine-derived organocatalysts is listed in Figure 1.10.

In 2004, Jørgensen and coworkers reported that the asymmetric α-chlorination of aldehydes proceeds well in the presence of C_2-symmetric diphenylpyrrolidine (**59**) as a catalyst using *N*-chlorosuccinimide (NCS) as a chlorinating agent [257]. Thereafter, they also explored its applicability to fluorination (**48**-type catalyst) and bromination (Scheme 1.21) [258].



cat **59** [Ref 257; X = Cl]
reagent: NCS (1.3 equiv)
in CH_2Cl_2, rt
30-99% yield
81-97% ee

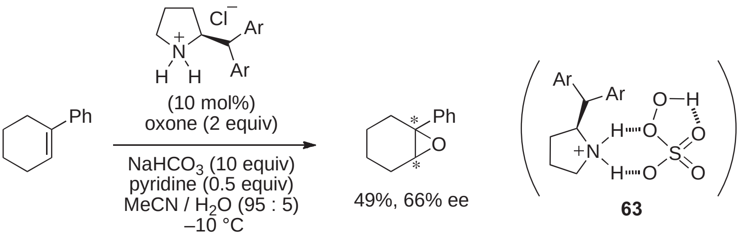
cat **48**-type [Ref 258a; X = F]
reagent: NFSI (1.5 equiv)
in toluene, 60 °C
78% yield
48% ee

cat **59** [Ref 258b; X = Br]
reagent: DBBC (0.5 equiv)
in CH_2Cl_2-pentane, –40 °C
72-95% yield
68-96% ee

Scheme 1.21

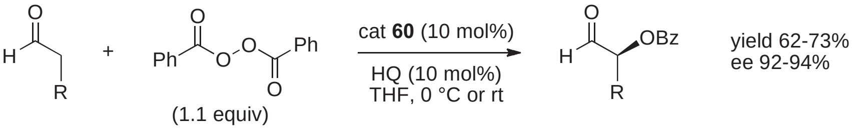
The synthetic utility of this method is clear: it provides easy manipulation of the products to give various important chiral building blocks such as chlorohydrins, epoxides, aziridines, amino acids, and amino alcohols [257–259], and is readily applicable to natural product synthesis [260].

Recently, considerable efforts have been made to discover new organocatalytic systems for asymmetric epoxidation. In 2003, Aggarwal and coworkers reported that the asymmetric epoxidation of olefins proceeded in good yields and with moderate enantioselectivities using Oxone® (Wako Chemicals, Osaka, Japan) as an oxidant in the presence of a **48**-type catalyst (Scheme 1.22) [261]. According to their proposal, the protonated ammonium salt species can act not only as a phase-transfer catalyst to carry the real oxidant species to the organic phase but also as a promoter to activate the chiral oxidant via hydrogen-bonding stabilization, as depicted in **63**.



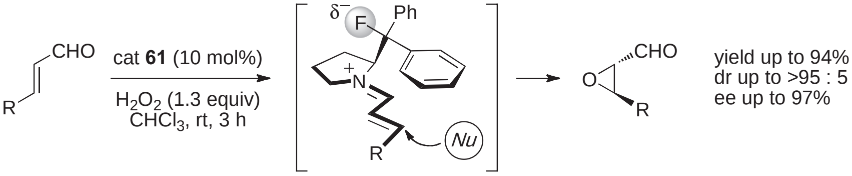
Scheme 1.22

On the other hand, Maruoka and coworkers achieved the asymmetric α-benzoyloxylation of aldehydes using the newly designed catalyst **60** (Scheme 1.23) [262].



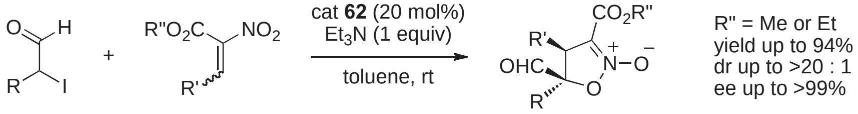
Scheme 1.23

Novel catalysts **61** and **62** have been invented to increase the catalytic activity by incorporation of an electronegative group (fluorine or azido) at the β-position relative to the NH group: an electrostatic interaction (or *gauche*-effect) between those groups might be favorable for stabilizing reactive intermediates [263–266]. For example, Gilmour and coworkers reported the **61**-catalyzed asymmetric epoxidation of α,β-unsaturated aldehydes (Scheme 1.24) [265].



Scheme 1.24

On the other hand, Zhong and coworkers found that the **62**-catalyzed system was effective for enantioselective [4+1]-annulation using 2-nitroacrylates and α-iodoaldehydes, to form *cis*-isoxazoline *N*-oxide derivatives in high yields and in high diastereo- and enantioselectivity (Scheme 1.25) [266].



Scheme 1.25

1.8
Conclusions

As described above, a great deal of success has been achieved in a wide variety of asymmetric transformations using a series of proline-related organocatalysts. This organocatalytic asymmetric synthesis offers several advantages over metal-catalyzed systems; for example, the ready availability of both enantiomers, ease of handling without the need for an inert atmosphere or anhydrous conditions, and inexpensive and non-toxic reagents. Unfortunately, however, significant limitations still remain to be overcome in this field, including high catalyst loading, a long reaction period, and harmful organic solvent media. We hope that this exceedingly attractive field in modern organic chemistry can lead to new, much more powerful catalysts as well as highly efficient organocatalyst-based asymmetric transformations.

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2

TMS-Prolinol Catalyst in Organocatalysis

Hao Jiang, Łukasz Albrecht, Gustav Dickmeiss, Kim L. Jensen, and Karl Anker Jørgensen

2.1

Introduction

The development of new catalysts and activation modes is one of the most fundamental tasks in asymmetric organocatalysis. A simple and efficient way to address the challenge of efficient stereoinduction in enantioselective transformations is the introduction of steric bulk in catalyst motifs to discriminate the enantiotopic faces of a prochiral molecule. At the infancy of organocatalysis, the pursuit of a general organocatalyst with broad applicability led to the discovery of several secondary amines as promising catalyst scaffolds for asymmetric functionalizations of carbonyl compounds [1]. However, issues related to limited reactivity, stereoselectivity, and generality were often encountered. This can be exemplified by diarylmethylpyrrolidine and diarylprolinol, which were shown to exhibit “orthogonal” characteristics regarding catalytic activity and selectivity in enamine-mediated processes (Scheme 2.1) [2].

The level of steric shielding offered by diarylmethylpyrrolidines was usually insufficient and only in rare cases provided high enantioselectivities, although good reactivity was observed for various transformations. Conversely, the diarylprolinol system was able to induce good stereocontrol, albeit with limited catalyst turnover. The main reason for catalyst inhibition was presumably the formation of a “parasitic” oxazolidine species. In an attempt to avoid this undesired pathway, the alcohol group of the diarylprolinol system was protected as the corresponding silyl ether [3]. Such an approach turned out to be successful, providing a sterically demanding yet highly active aminocatalyst. Although this catalyst scaffold was initially designed to promote enamine-mediated α-functionalizations, various additional enantioselective reactions via other distinct reaction pathways, such as iminium ion, dienamine, and trienamine activation, have been realized. From a library of synthesized diarylprolinol silyl ethers, two of them, **1a** and **1b**, have proven to be highly general catalysts (Scheme 2.1) [4]. Herein, structural features, mechanistic aspects, and the origin of stereoinduction for this class of aminocatalysts are discussed. Furthermore, representative contributions are highlighted.

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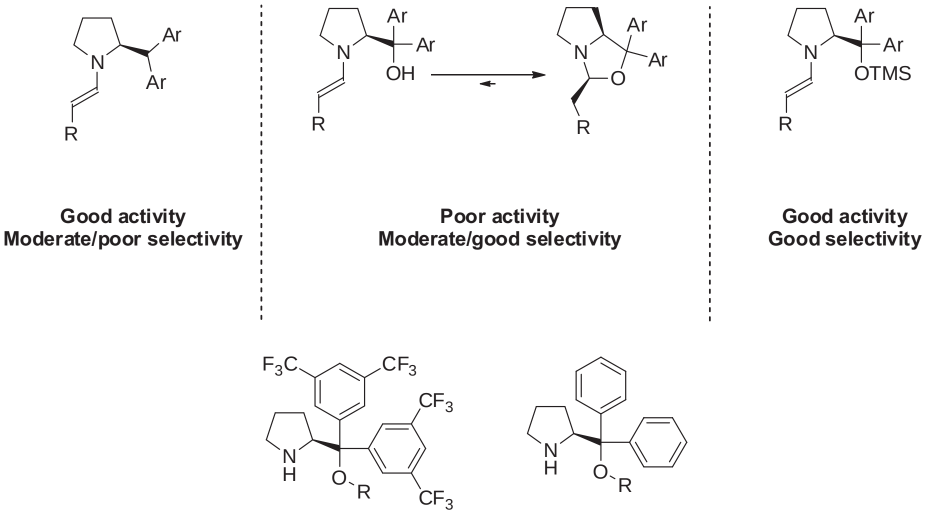


1a: R = TMS
1c: R = TES

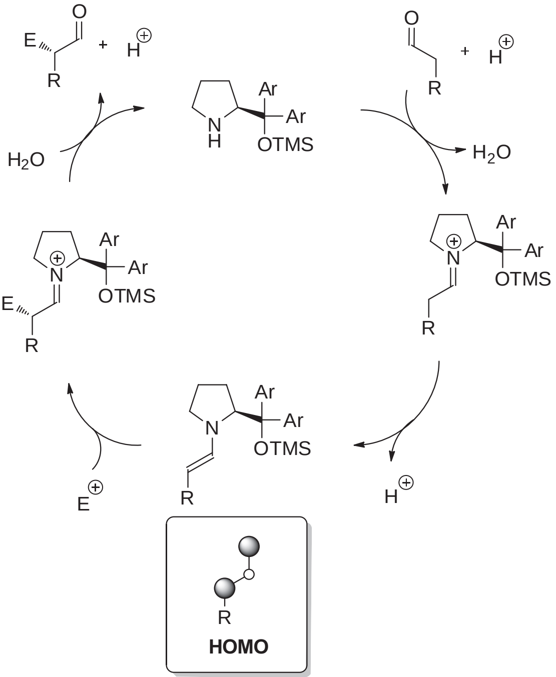
1b: R = TMS
1d: R = TES
1e: R = TBS

Scheme 2.1 Rational catalyst design and the most general and applied catalysts.

2.2
Enamine Activation

The catalytic cycle of enamine-mediated α-functionalizations is initiated by the condensation of the diarylprolinol aminocatalyst and the aldehyde, forming an iminium ion, which after deprotonation/isomerization gives the nucleophilic enamine species (Scheme 2.2) [5]. The enamine has increased reactivity compared to the corresponding enol due to its higher-energy HOMO (highest occupied molecular orbital). Furthermore, the iminium-ion/enamine equilibrium favors the enamine, thereby facilitating the presence of a larger amount of the reactive species in solution (in contrast to the aldehyde/enol equilibrium where the aldehyde is generally favored). The enamine may then attack an electrophile, the approach of which is governed by the bulky substituent on the catalyst, with the attack from "below" (*Si*-face attack) being preferred. Finally, hydrolysis delivers the enantiomerically enriched product and releases the catalyst.

To account for the structure of the reacting enamine and the observed stereochemical outcome, calculations on the different possible intermediates have been performed, applying the enamine derived from catalyst **1a** and 3,3-dimethylbutanal as a model substrate [6]. In principle, four different enamine structures can be imagined as depicted in Figure 2.1. Both (*Z*)-forms are significantly higher in energy than the corresponding (*E*)-isomers, which is presumably attributed to steric repulsion between the ^{t}Bu substituent and the methylene protons of the pyrrolidine ring in (*Z*-*s*-*trans*)-**2** or the OTMS- and aryl-substituents in (*Z*-*s*-*cis*)-**2.**



Scheme 2.2 Mechanism for asymmetric organocatalytic α-functionalization of aldehydes.

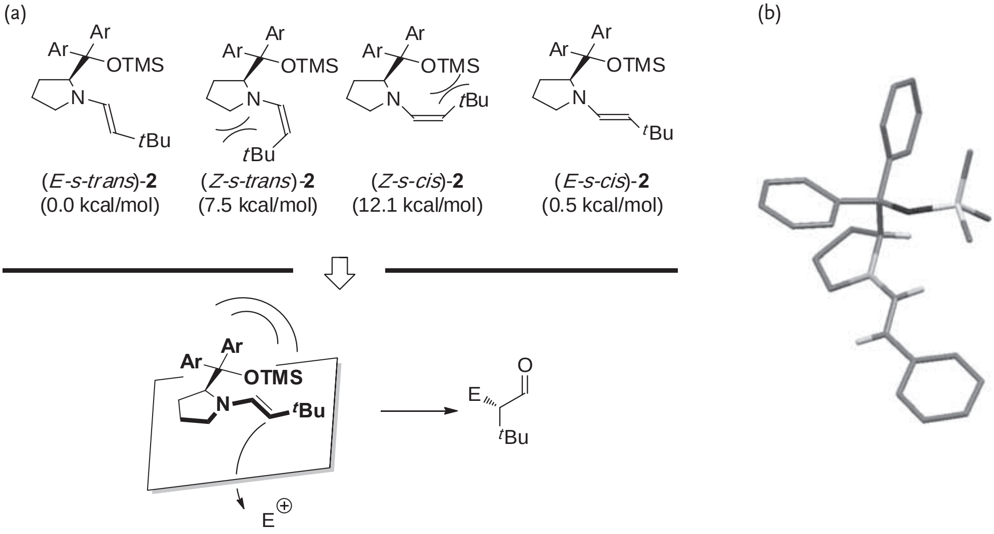
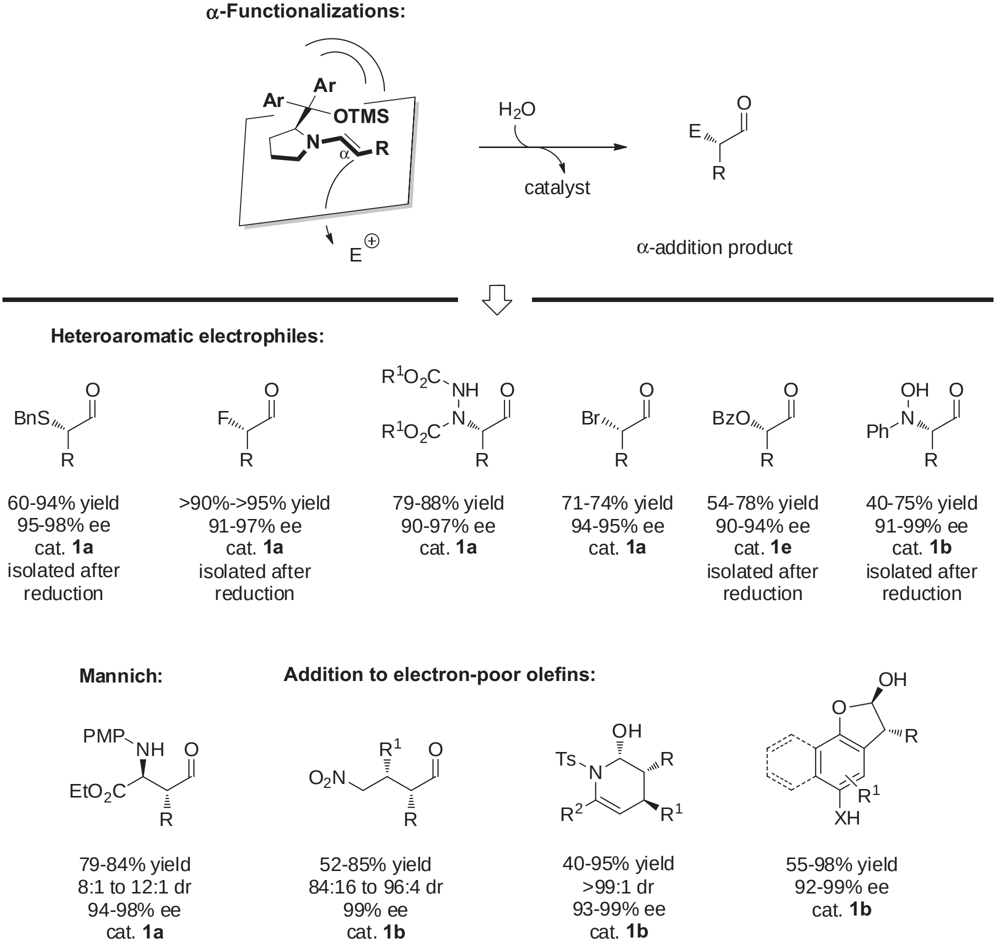


Figure 2.1 (a) Calculations on possible enamine intermediates; (b) X-ray structure of enamine intermediate. Seebach, 2008, CCDC 695934 (most hydrogens omitted for clarity).

The two (*E*)-isomers have lower, comparable energies, suggesting these are the predominant catalytic intermediates. The computational findings are further supported by X-ray studies on model substrates by Seebach *et al.* [7]. Moreover, NMR spectroscopic studies by Gschwind *et al.* of the similar proline-catalyzed self-aldol reaction of propionaldehyde in DMSO verify the presence of an (*E-s-trans*)-enamine as the only observable intermediate [8].

Notably, the slight ground state energy difference between (*E-s-trans*)-**2** and (*E-s-cis*)-**2** does not account for the high levels of stereocontrol generally observed with this catalytic system. To explain this, representative calculations on the most probable transition states in the selective fluorination of 3,3-dimethylbutanal with NFSI catalyzed by **1a** were performed [6]; in this context, in particular the transition state energies arising from NFSI attack from "below" on (*E-s-trans*)-**2** and (*E-s-cis*)-**2** would be of interest. The calculations show an energy difference of 2.4 kcal mol^{-1}



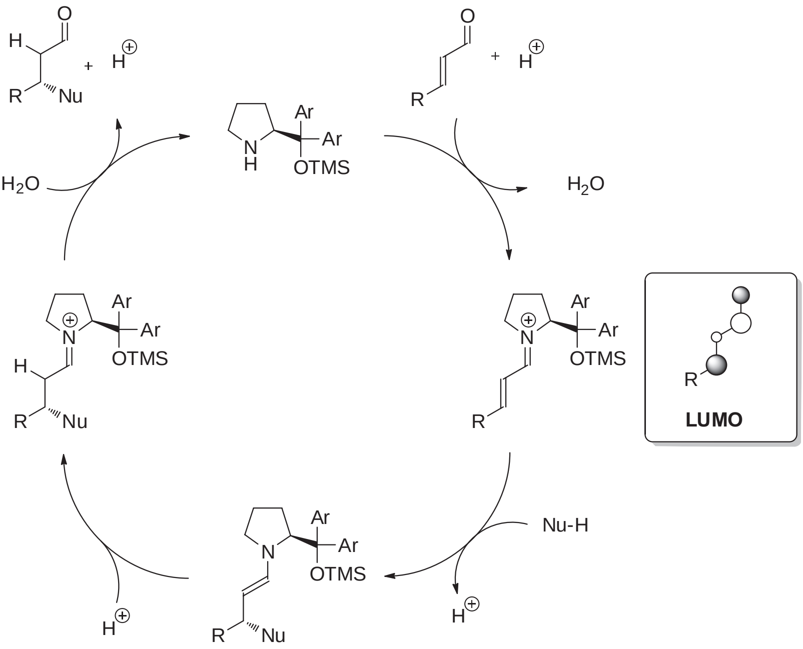
Scheme 2.3 Representative examples of α-functionalizations.

favoring attack on (*E-s-trans*)-**2**, which accounts for the selectivity experimentally observed in the reaction. This difference may be explained by the increasing steric interaction between the *tert*-butyl group and the large bulk of the catalyst, as the α-carbon develops sp^3-character during functionalization [an interaction that is more pronounced for the reaction involving (*E-s-cis*)-**2** than that of (*E-s-trans*)-**2**]. Notably, attack on (*E-s-trans*)-**2** from "above" (*Re*-face attack) is energetically significantly unfavored (9.5 kcal mol^{-1}), underlining the efficient face-shielding provided by the catalysts.

The diarylprolinol silyl ether system was initially applied for the asymmetric α-sulfenylation of aldehydes. Since then, it has proven its usefulness in combination with a large number of heteroatom- and carbon-based electrophiles for asymmetric α-functionalizations of aldehydes (Scheme 2.3) [2, 3, 9].

2.3
Iminium-Ion Activation

Complementary to the enamine-based reactions, the diarylprolinol silyl ether catalysts can be applied for activation of α,β-unsaturated aldehydes toward conjugate additions through iminium-ion-induced processes. Mechanistically, this conceptually different activation mode draws close parallels to the enamine chemistry (Scheme 2.4) [5]. The secondary aminocatalyst condenses with the enal to form



Scheme 2.4 Mechanism for asymmetric, organocatalytic β-functionalization of α,β-unsaturated aldehydes.

the reactive iminium-ion intermediate, which can be considered an organocatalytic alternative to conventional Lewis acid activation of α,β-unsaturated carbonyl compounds. Addition of a nucleophile leads to an enamine intermediate, which is in equilibrium with its corresponding iminium ion. As in the case for enamine-based reactions, the iminium ion is hydrolyzed to release the product and the catalyst as the last step of the catalytic cycle. Two things are worth mentioning in terms of selectivity: the catalyst not only shields one of the enantiotopic phases of the enal, it also ensures excellent chemoselectivity, affording 1,4-adducts as the sole products.

The key feature of iminium-ion activation is the lowering of the LUMO (lowest unoccupied molecular orbital) energy, whereby an increased reactivity of the unsaturated system towards nucleophilic addition is obtained. To better understand the mechanism and kinetics of the iminium-ion formation, several experimental studies and calculations have been performed. Often the reactions are accelerated by the addition of Brønsted acid co-catalysts, which presumably assist the initial condensation. This indicates that the condensation is the rate-determining step in these reactions. In a recent study by Mayr [10], the electrophilicity of different iminium ions obtained from various aminocatalysts and cinnamaldehyde was investigated experimentally (Figure 2.2).

By applying nucleophiles with known nucleophilicities, the electrophilicity parameters (*E*) could be determined by kinetic experiments. Interestingly, in light of the increased steric bulk, the diarylprolinol catalyst-derived iminium ion was found to be 20 times more reactive than the one formed from pyrrolidine [10]. This increased reactivity is attributed to the electron-withdrawing effect of the aryl substituents. Notably, the intermediate derived from the imidazolidinone-based catalyst showed the highest electrophilicity.

As for enamine-mediated α-functionalizations, the excellent enantiocontrol of iminium-ion-induced processes is provided by the sterically demanding side-chain of the catalyst, which forces the incoming nucleophilic reagent to approach the iminium ion from the least hindered face. Until recently, it was commonly accepted that the effective facial shielding of the catalyst was exerted by the aryl substituents, which might be involved in π-stacking interactions with the carbon–carbon double bond of the conjugated system. However, recent detailed studies by means of X-ray crystallography, NMR spectroscopy, and theoretical calculations

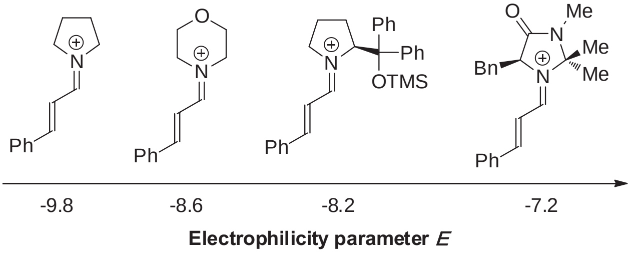
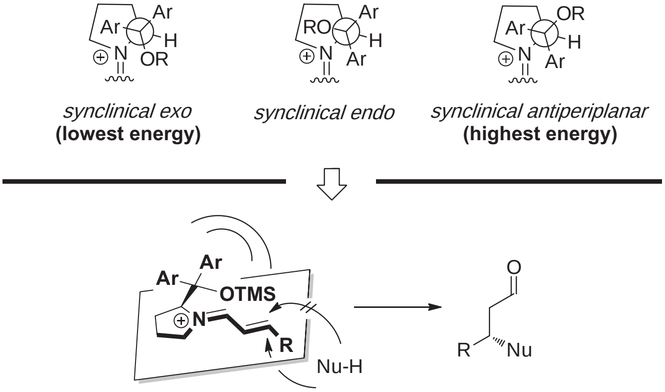


Figure 2.2 Relative electrophilicities of selected iminium ions.

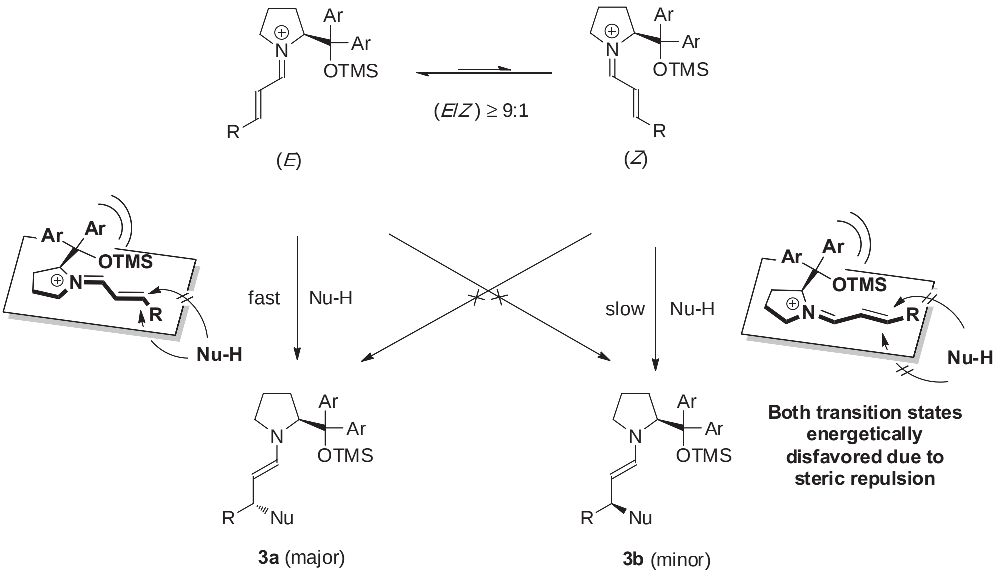
clarified the picture and shed some light on the origins of the catalyst shielding (Scheme 2.5) [7, 11]. It was shown that the *synclinical exo* conformation of the catalyst-bound iminium ion is lowest in energy (≥3.2 kcal mol^{-1} more stable than the *synclinical endo* conformer according to theoretical calculations). This result indicates that the shielding effect responsible for facial discrimination and as a consequence the high enantioselectivity of the reactions is exerted by the OTMS-substituent. Furthermore, in the case of catalysts bearing substituents in the *meta*-position of the phenyl rings, the *meta*-substituents contribute additionally to the shielding of the carbon–carbon double bond [7, 11a]. This explains why, in most cases, the 3,5-bis(trifluoromethyl)phenyl-substituted catalyst **1a** ensures higher selectivities than the corresponding diphenyl-substituted catalyst **1b.** The additional shielding effect exerted by the *meta*-substituents presumably also accounts for its lower reactivity.



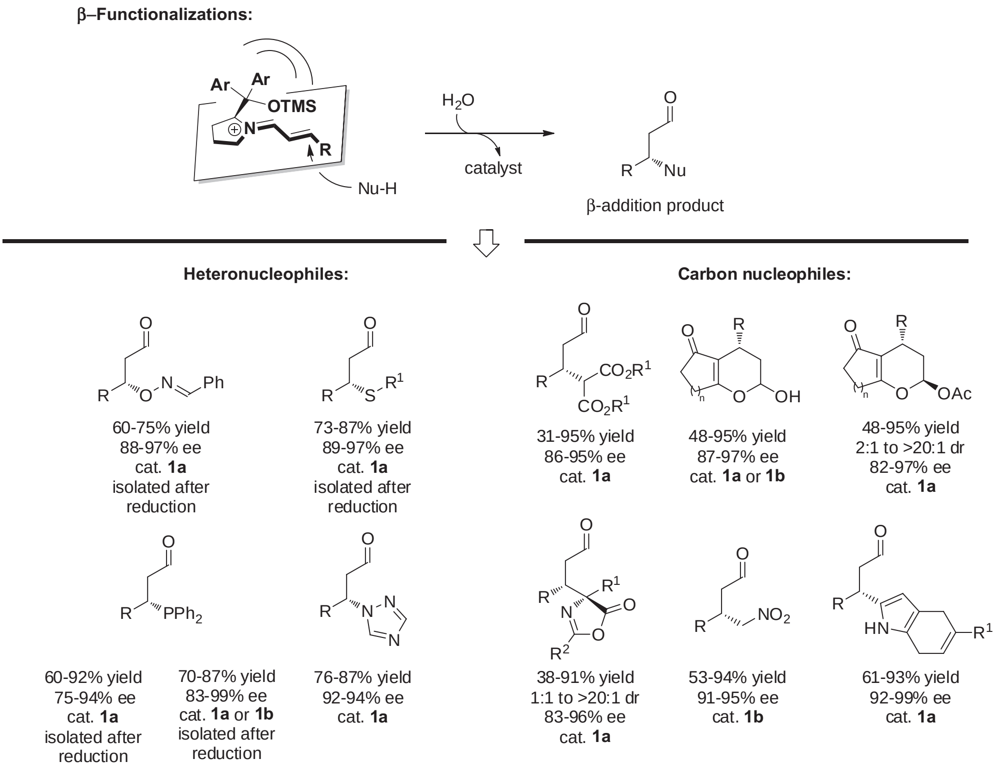
Scheme 2.5 Conformations and shielding effect of diarylprolinol trimethylsilyl ether-derived iminium ions.

An important aspect of the iminium-ion chemistry relates to the fact that under given reaction conditions the corresponding iminium ions exist as mixtures of (*E*)- and (*Z*)-isomers around the carbon–nitrogen double bond (Scheme 2.6). This is in contrast to the generally assumed scenario involving the (*E*)-configured intermediate as the only present reactive species (notably, in this context, the nucleophilic addition to oppositely configured iminium ions leads to the formation of opposite enantiomers of the final products and should result in enantiomeric excess deterioration). In terms of composition of the abovementioned (*E*/*Z*)-mixtures, theoretical studies performed on the intermediate derived from **1a** and *trans*-2-pentenal revealed that the (*E*)-isomer is 1.6 kcal mol^{-1} more stable than the corresponding (*Z*)-isomer [such an energy difference corresponds to approximately a 9 : 1 (*E*/*Z*)-ratio] [12]. More recently, thorough experimental studies on the composition of iminium ions derived from diarylprolinol trimethylsilyl ether aminocatalysts by means of NMR spectroscopy confirmed the presence of noticeable amounts of the undesired (*Z*)-isomer in the reaction mixtures that depended strongly on experimental parameters ([*E*/*Z*] ratio ranging from 92 : 8 to 93 : 7 for catalyst **1a** and 97 : 3 for catalyst **1b** [11b]). However, despite the presence of the (*Z*)-isomer in the reaction mixtures, high enantioselectivities are possible to obtain in most cases. This experimental observation can be easily rationalized by taking into account that the iminium-ion-mediated reactions proceed in agreement with the Curtin–Hammett principle. Accordingly, the more stable (*E*)-isomer reacts faster, implying that the transition state leading to the minor product from the (*Z*)-isomer is higher in energy. As a consequence, the enantioenrichment of the final product does not correspond to the (*E*/*Z*)-ratio of the iminium-ion intermediate.

The generality of iminium-ion-mediated reactions catalyzed by diarylprolinol silyl ethers is illustrated in Scheme 2.7. Sulfur- [13], oxygen- [14], phosphorus- [15], nitrogen- [12], and carbon-centered [16] nucleophiles can be efficiently added to iminium-ion-activated α,β-unsaturated aldehydes. In most cases high yields are obtained even for the addition of hard nucleophiles such as oximes. Furthermore, these reactions are characterized by their full chemoselectivity. Despite the possibility of undergoing 1,2-addition, this catalytic system ensures selective formation of 1,4-adducts. Finally, in most cases excellent enantioselectivities exceeding 90% ee are obtained, confirming the superior facial shielding provided by diarylprolinol aminocatalysts. Importantly, this simple, yet fundamental organocatalytic transformation affords access to various enantiomerically enriched building blocks



Scheme 2.6 Influence of (*E*/*Z*)-ratios of iminium ions on the stereochemical outcome of the reactions.

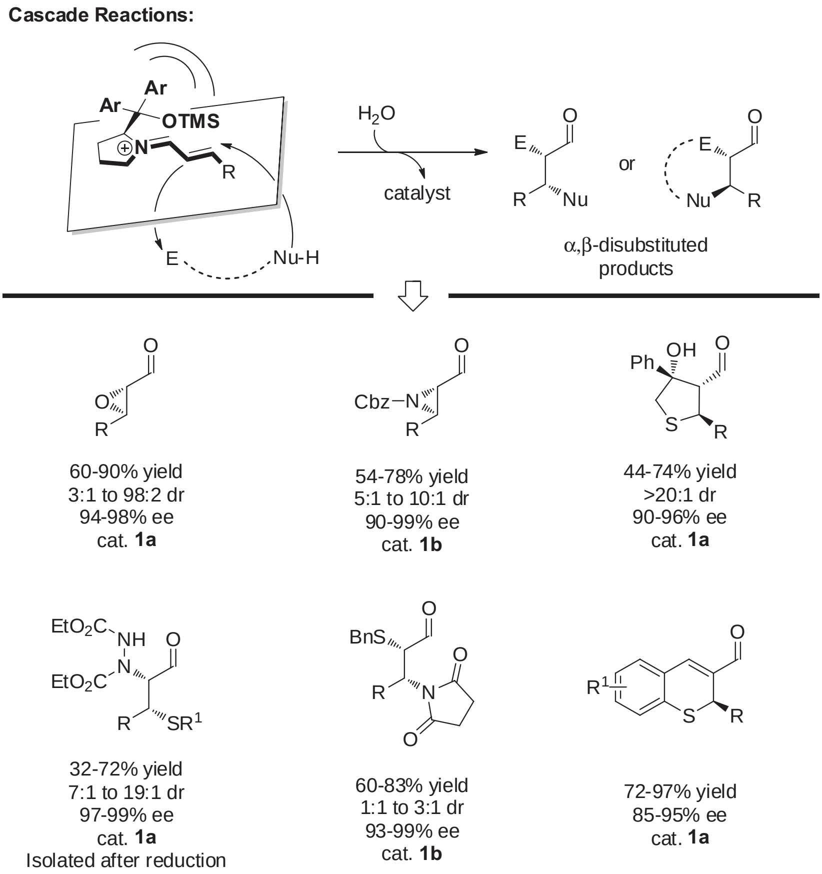


Scheme 2.7 Representative examples of β-functionalizations.

that have found applications in target-oriented syntheses of molecules relevant for the life-science industry.

2.4
Cascade Reactions

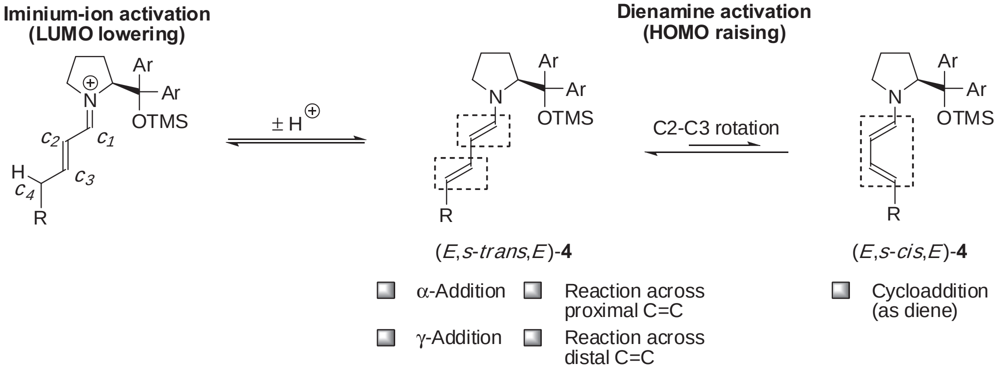
The ability of the diarylprolinol catalysts to participate in both enamine- and iminium-ion activations makes them ideal for the sequential addition of nucleophiles and electrophiles through cascade catalysis (Scheme 2.8). Conjugate addition of a nucleophile to the iminium ion forms a transient enamine intermediate **3**, which can effectively react with an electrophile in the α-position, forming an α,β-disubstituted adduct. This process commonly proceeds to afford the products in good yields and with high enantio- and diastereoselectivities. If the nucleophile and electrophile are part of the same molecule, cyclic products are obtained. The cascade concept has been widely explored and some illustrative examples are given below [13, 17].



Scheme 2.8 Representative examples of cascade reactions.

2.5
Dienamine Activation

In the light of their outstanding capacity of promoting stereoselective α- and β-functionalizations as well as cascade reactions, the silyl-protected diarylprolinol system is arguably warranted a spot among the most useful and privileged catalyst structures in organocatalysis. With that said, the potential of these catalyst structures is not only limited to enamine and iminium-ion type reactions, although these remain the two most abundant and well-developed activation modes promoted by this aminocatalyst family. One of the more recent discoveries within aminocatalysis involves the generation of reactive catalyst-bound dienamine species from α,β-unsaturated aldehydes, thereby activating enals toward reaction pathways other than the iminium-ion route (Scheme 2.9) [18]. It shall be revealed that in this type of activation mode – dienamine activation – the diarylprolinol system also prevails.

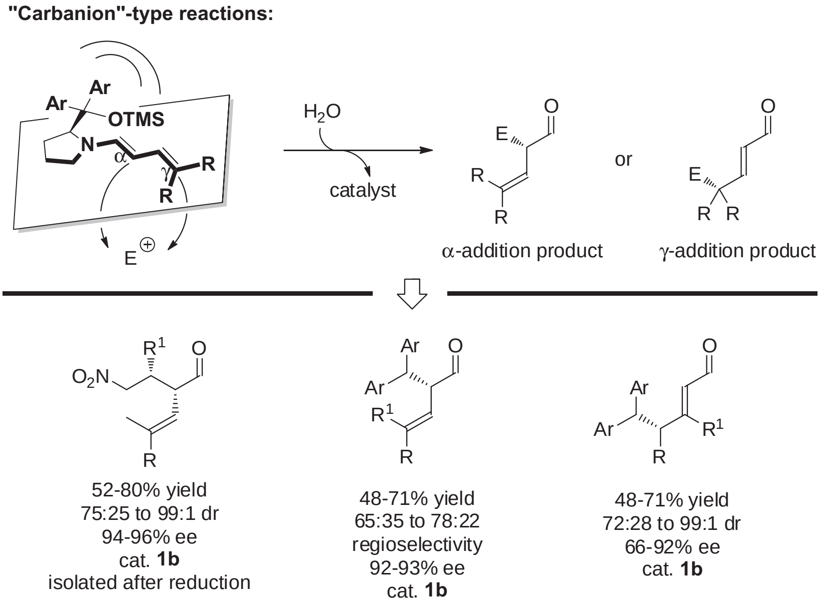


Scheme 2.9 Deprotonation/protonation differentiates iminium-ion and dienamine activation.

Notably, the reactive species in iminium-ion and dienamine activation arises from common starting materials, an enal and an aminocatalyst, while only being differentiated by a deprotonation/protonation step. In the presence of available γ-protons (C4), the specific reaction setup selects the dominant pathway, while if such protons are absent then iminium-ion activation remains as the only possibility. In dienamine-mediated reactions, the diarylprolinol aminocatalysts serve a dual purpose: (i) participating in the generation of a reactive catalyst-bound dienamine species, thereby providing activation via the HOMO raising principle; (ii) offering the required face-differentiation for good stereoinduction. At this point, it should be emphasized that dienamine in contrast to enamine or iminium-ion activation enables various different reaction pathways, which herein will be named "carbanion"-, "ene"-, or "diene"-type reactivity. In brief, the two "ene" fragments will either individually or jointly react with suitable reactants, hence leading to many possible outcomes. However, common for all reaction paths is the fact that the central catalyst structure of this chapter – the silyl-protected diarylprolinol – promotes as well as governs stereoselectivity in these reactions with great efficiency.

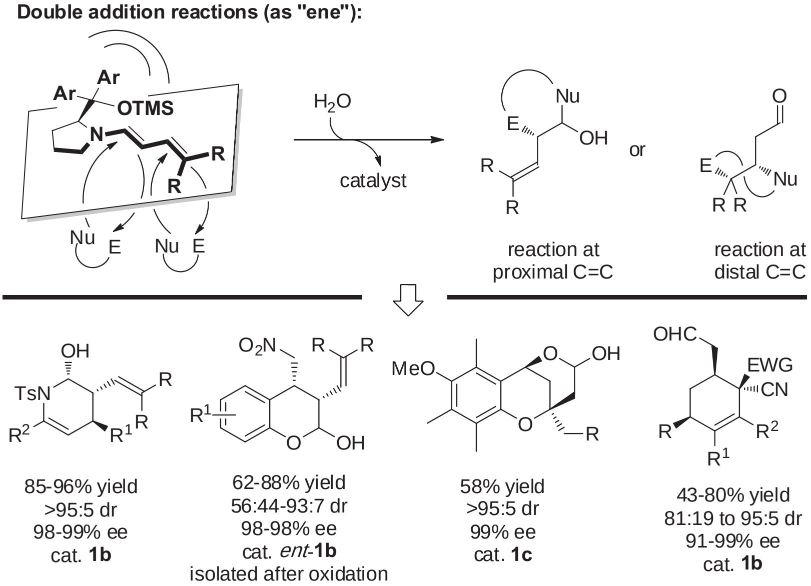
The high levels of stereoinduction provided by the diarylprolinol system in dienamine activation originated in the proficiency by which the bulky stereocontrolling group of the aminocatalyst provides facial shielding and conformational restriction in the reactive catalyst-bound dienamine species. While the face-discrimination aspect is very similar to that in enamine and iminium-ion activation and will not be discussed further, the possible conformations the dienamine may adopt deserve attention. As illustrated in Scheme 2.9, the all-*trans* (*E,s-trans,E*)-**4** is undoubtedly the energetically most stable conformation of the diarylprolinol-derived dienamine species. It is believed that most dienamine-mediated reactions, such as α-, and γ-addition as well as cycloadditions (as "ene") proceed via the intermediacy of this conformation (Scheme 2.9, middle). A change of this geometry via either a single bond rotation (giving rotamers) or a protonation/deprotonation sequence [giving (*E*/*Z*)-isomers] is always accompanied by an energetic barrier as well as the formation of higher energy conformations due to increased steric repulsion. Despite the limited amount of theoretical studies on dienamine systems, it is anticipated that most of these conformers/isomers are unlikely to participate in reactions due to high ground state or transition state energies [19]. However, one important rotamer, (*E,s-cis,E*)-**4**, resulting from C2–C3 single bond rotation should be emphasized since it accounts for the unique "diene"-type reactivity in dienamine activation (Scheme 2.9, right-hand side). In the following, selected examples of dienamine-mediated reactions will be discussed.

The "carbanion"-type reactivity of dienamine activation can be promoted by a silyl-protected diarylprolinol catalyst in the presence of reactive electrophilic species, such as nitroolefins or diarylmethanols (Scheme 2.10) [20]. Although both direct addition (α-addition) and vinylogous addition (γ-addition) are viable reaction pathways, the α-reactivity is the more typical one and usually provides better selectivities due to more effective shielding of the α-position by the aminocatalyst. Interestingly, the α-/γ-selectivity of dienamine-mediated "carbanion"-type addition reactions seems to be strongly influenced by the substitution pattern of the enal reactant. For example, it was demonstrated that γ,γ-disubstituted enals favor the α-addition product, while γ-functionalization is the predominant reaction pathway for γ-monosubstituted enals.



Scheme 2.10 Representative examples of "carbanion"-type reactivity via dienamine activation.

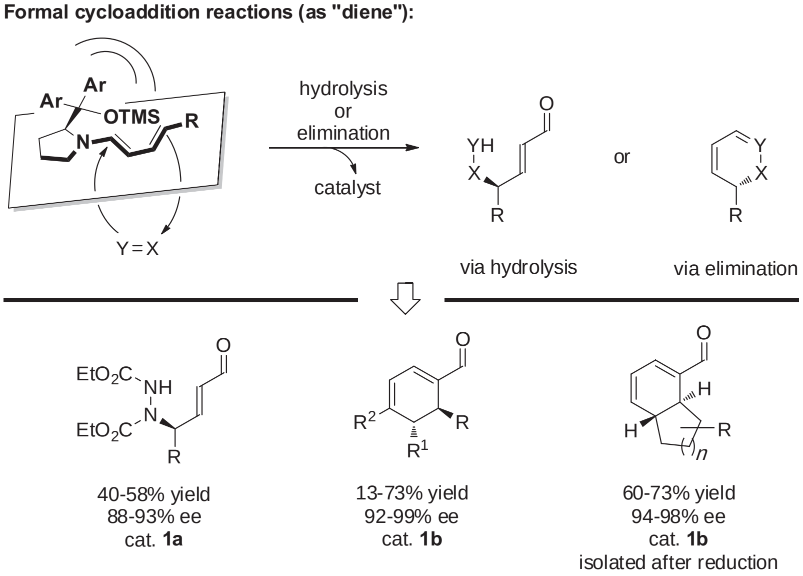
In the presence of suitable reaction partners, (*E,s-trans,E*)-**4** may also undergo double addition reactions (electrophilic-nucleophilic) across one of its two "ene"-fragments, thereby affording more complex molecular structures (Scheme 2.11).



Scheme 2.11 Representative examples of "ene"-type reactivity via dienamine activation.

Given the excellent ability of the diarylprolinol catalyst to secure facial discrimination and conformational restriction, high stereoselectivities are often achieved in these reactions. Selective reaction at the proximal double bond of (*E*,*s*-*trans*,*E*)-**4** has, for example, been accomplished, resulting in formal inverse-electron-demand hetero-Diels–Alder reactions [21]. Alternatively, several reports have concluded that selective targeting of the distal electron-rich alkene motif of the catalyst-bound intermediate is also viable [22].

Finally, instead of reacting across an isolated alkene unit the catalyst-bound dienamine species has the possibility to react as an electron-rich diene fragment in Diels–Alder reactions (Scheme 2.12). As previously mentioned, a C2–C3 single bond rotation is required for such reactivity. Computational data revealed that for the dienamine species generated by **1a** and *trans*-2-hexenal, the C2-C3 rotation has a barrier of only 7.5 kcal mol^{-1} [19]. Moreover, it was illustrated that in the presence of suitable reactants, such as azadicarboxylates, the transition state for a Diels–Alder pathway via the (*E*,*s*-*cis*,*E*)-conformation has a much lower transition state energy when compared to a direct α- or γ-addition to (*E*,*s*-*trans*,*E*)-**4**. In accordance with all previously described reactions in this chapter, the bulky substituent of the diarylprolinol catalyst effectively blocks one of the diene faces towards approaching dienophiles, thereby leading to the formation of highly enantioenriched cycloadducts. However, an important limitation of this type of dienamine-mediated cycloaddition is the simultaneous bond formation at the C1 position, thereby possibly inhibiting the catalyst turnover. The use of heteroatom-centered dienophiles such as azadicarboxylates provides one solution to this problem, hence allowing

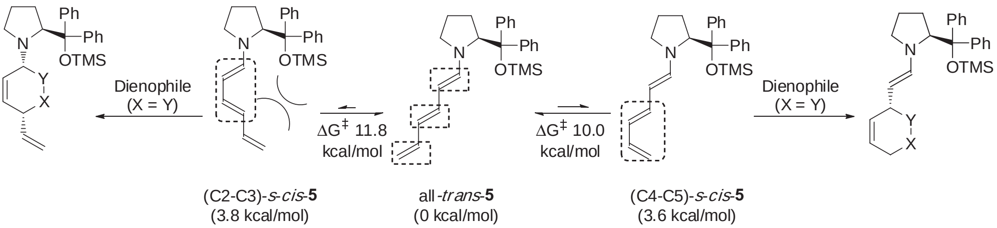


Scheme 2.12 Representative examples of "diene"-type reactivity via dienamine activation.

liberation of the diarylprolinol catalyst via simple hydrolysis. When a carbon–carbon bond is formed at the C1 center, catalyst turnover can only be maintained via an eliminative pathway [23]. However, this alternative can be tedious and will require the presence of an acidic neighboring proton. Moreover, further unsaturation will accumulate in the product molecule.

2.6
Trienamine Activation

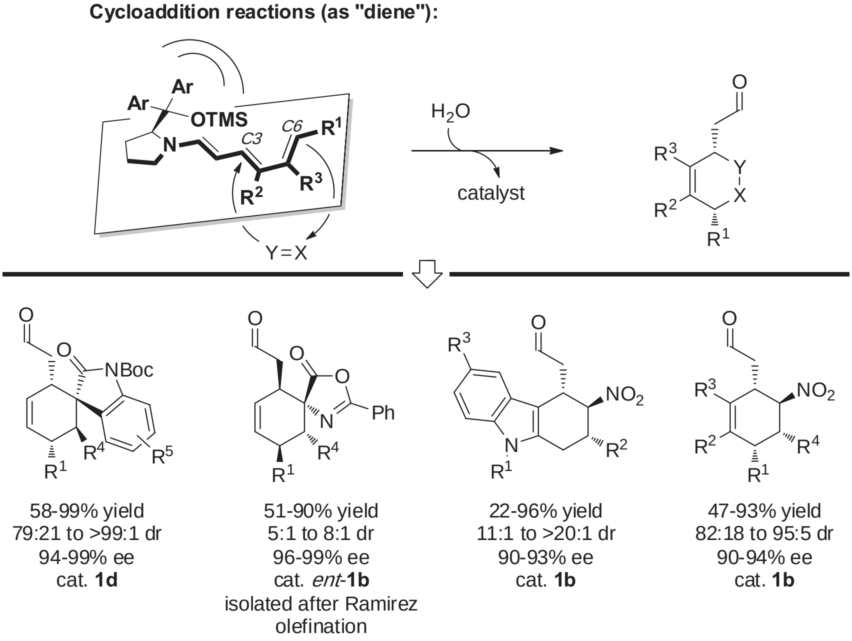
More recently, it was discovered that the HOMO-raising concept of enamine and dienamine activation can be further extended to incorporate polyconjugated enals, such as 2,4-dienals, which upon condensation with the diarylprolinol catalyst may form a geometrically well-controlled and face-discriminated trienamine species [24]. In accordance with the dienamine case, the all-*trans*-configured conformation of the catalyst-bound trienamine species has the lowest ground state energy, as calculated for all-*trans*-**5** (Scheme 2.13). From this intermediate, a range of "carbanion"- or "ene"-type reactions may be anticipated; however, due to the short time since the discovery of trienamine activation, successful reactions in this domain are yet to be reported. In addition, two single bond rotations around the C2–C3 and C4–C5 connectivities would result in the formation of two different *cis*-diene fragments, which both have the potential of participating in [4+2]-cycloadditions. Experimentally, only reaction across the remote diene system [via



Scheme 2.13 Possible conformers and sites of reaction of the trienamine intermediate.

(C4–C5)-*s-cis*-**5**] has been observed, which could be a result of the Curtin–Hammett principle.

An intriguing aspect of trienamine-mediated reactions is the ability of the catalysts to offer sufficient stereoinduction at the remote C6 center. However, due to the concerted nature of the Diels–Alder reaction, it is suggested that the steric shielding at C3, where a new bond is formed as well, could indirectly extend the chirality relay of the bulky substituent of the aminocatalyst to the distant C6 center, hence providing the experimentally observed excellent enantioselectivities for such reactions (Scheme 2.14).



Scheme 2.14 Trienamine-mediated Diels–Alder reactions.

2.7
Summary and Conclusions

This chapter describes the synthetic usefulness, efficiency, and selectivity as well as mechanistic aspects of the diarylprolinol silyl ether system in various reactions of aldehydes. Although the catalyst scaffold was originally designed for one specific reaction, the enantioselective α-sulfenylation of aldehydes, it proved general and useful in a series of functionalizations and activation modes. The enamine-mediated transformations of saturated aldehydes have resulted in the introduction of different functionalities at the α-position of aldehydes in a highly stereoselective manner. Complementary to the enamine-mediated activations, α,β-unsaturated aldehydes can be effectively functionalized via conjugate addition through iminium-ion-mediated processes. The ability of these catalysts to participate in various enamine- and iminium-ion-induced reactions makes them ideal for the sequential addition of nucleophiles and electrophiles in a cascade manner, thereby giving access to products having at least two stereocenters. Later, the HOMO-activation concept of enamine-mediated processes was extended to include α,β-unsaturated aldehydes and 2,4-dienals. After condensation of aldehyde and aminocatalyst, a dienamine/trienamine species is formed, which can undergo various stereoselective reactions, thereby effectively functionalizing remote positions of the aldehydes.

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3

Non-Proline Amino Acid Catalysts

Li-Wen Xu and Yixin Lu

3.1

Introduction

Ever since the rebirth of modern asymmetric organocatalysis in the year 2000, proline has been regarded as one of the most prominent catalysts [1]. Among the natural amino acids, proline is the only one with a secondary amino group, and such a distinct structural feature makes proline and its structural analogs unique in asymmetric organic catalysis [2]. In contrast to the enormous popularity of proline in asymmetric catalysis, non-proline primary amino acids were virtually neglected in the early 2000s. Such negligence is rather astonishing, particularly in view of the importance of primary amino acids in enzyme catalysis and beautiful applications of primary amino acids in asymmetric synthesis demonstrated by chemists a few decades ago. Primary amino acid residues are known to play indispensible roles in enzymatic reactions. For instance, type I aldolases, decarboxylases, and dehydralases all make use of a key lysine or threonine residue at their active sites [3]. In 1971, Eder, Sauer, and Wiechert showed that phenylalanine was a good catalyst for intramolecular aldol reactions [4]. In their investigations, Hajos and Parrish also examined the feasibility of utilizing phenylalanine as a catalyst in an asymmetric intramolecular aldol reaction [5]. Subsequently, Buchschacher and coworkers reported primary β-amino acids, such as β^3-homophenylalanine, and γ-amino acids were effective catalysts for intramolecular asymmetric aldol condensations [6]. More recently, Davies, Smith, and coworkers found that β-amino acid (1*R*,2*S*)-cispentacin promoted the Hajos–Parrish–Eder–Sauer–Wiechert reaction with levels of enantioselectivity comparable to or higher than those of proline-catalyzed reactions [7]. By combining phenylalanine with $HClO_4$, Danishefsky *et al.* prepared the intramolecular aldol product in high optical purity; this result is particularly intriguing in view of the disappointing low stereoselectivity attainable with proline [8]. Thereafter, more examples employing a combination of phenylalanine with either $HClO_4$ or camphorsulfonic acid to effect asymmetric intramolecular aldol reactions in the steroid synthesis were disclosed by Tsuji [9], Hagiwara [10], and Corey [11]. Moreover, it is noteworthy that the amino acid-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert reaction found wide applications

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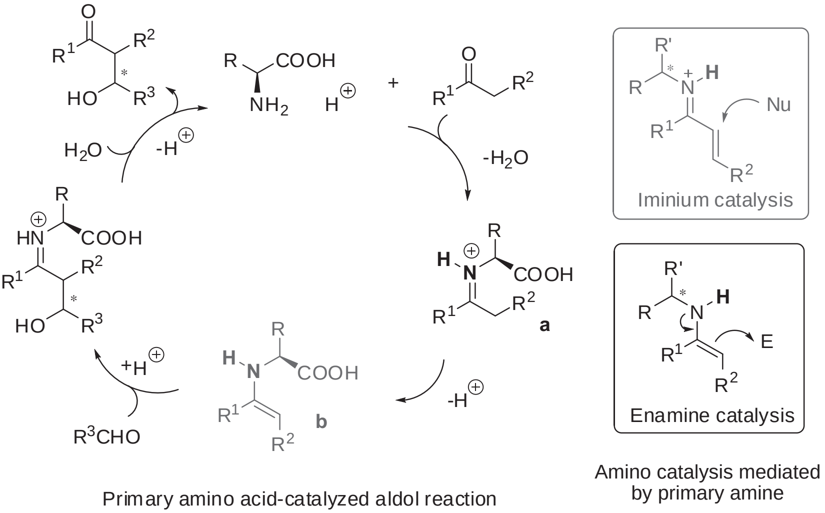
in total synthesis [12]. These early studies firmly established the usefulness and power of primary amino acids in asymmetric synthesis, suggesting their potential applications in a broader scope of reactions.

3.2
Primary Amino Acids in Amino Catalysis

In their seminal report published in 2000, List, Barbas, and Lerner disclosed that L-proline was an effective catalyst for the direct intermolecular aldol reaction [1a]. In the same year, MacMillan reported the first highly enantioselective Diels–Alder reaction via iminium activation [13]. Following these milestone discoveries, asymmetric amino catalysis progressed explosively in a short period of time, and a huge number of proline analogs were developed and utilized for a wide range of organic transformations. Surprisingly, primary amino acid catalysts did not occupy a place in this early “gold rush”; there were practically no reports on primary amino acids in enamine/iminium catalysis in the early 2000s. In fact, in the initial report by List *et al.*, primary amino acids, such as valine and phenylalanine, were shown to be very poor catalysts for the aldol reaction [1a]. These can all be well rationalized, as it has been long thought that a secondary enamine is better stabilized than its primary counterpart by hyperconjugation, and a primary amine yields an imine as a predominant form. However, one should not forget that Nature elegantly makes use of primary amino acid-derived enamine intermediates in enzyme catalysis. Moreover, the early examples by synthetic chemists also demonstrated the feasibility of primary amine-mediated enamine catalysis for intramolecular reactions. Effective generation of the enamine intermediates from primary amine-derived imines is a key issue, if one wants to make use of chiral primary amines for intermolecular reactions via the enamine mechanism.

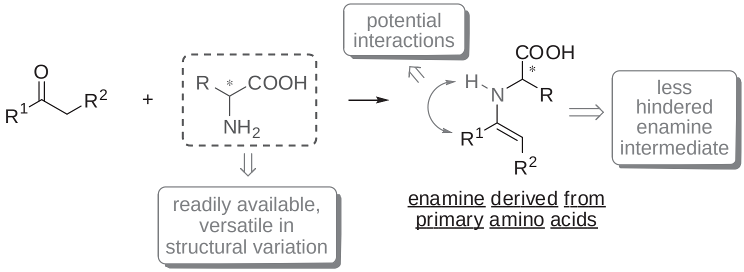
The catalytic cycle for a primary amino acid-promoted aldol reaction is illustrated in Scheme 3.1. For the reaction to take place via the enamine mechanism, effective creation of the enamine intermediate from an imine is a prerequisite, and cleavage of the α-proton of imine (**a**) affords enamine species (**b**). However, the N–H proton in iminium **a** may compete with the α-proton in the desired tautomerization process, thus making enamine generation less readily. Wong and coworkers discovered that water molecules participated in a proton relay to effectively convert a lysine-derived imine into its enamine form at the enzyme active site [14]. Subsequently, Barbas and Amedjkouh also independently disclosed the importance of a small amount of water for enamine formation in organic solvents [15]. Collectively, these investigations demonstrated the feasibility of employing primary amino acids in enamine catalysis, provided the key enamine intermediates could be effectively generated.


R–COOH NH2 H⊕
-H2O
a
b
-H⊕
+H⊕
R3CHO
H2O
-H⊕
Iminium catalysis
Nu
Enamine catalysis
E
Primary amino acid-catalyzed aldol reaction
Amino catalysis mediated by primary amine

Scheme 3.1 Primary amino acids/amines in amino catalysis.

3.3
Primary Amino Acid-Derived Organic Catalysts

It was not until 2004/2005 that primary amino acids were investigated and recognized as effective organic catalysts in asymmetric amino catalysis, particularly in enamine catalysis. Compared with proline and its analogs, primary amino acids have some distinct advantages in enamine activation. As shown in Scheme 3.2, the N–H group in the enamine intermediate may be engaged in potential interactions with suitable substrates, facilitating stereochemical control during the reaction. Furthermore, the enamine intermediates derived from primary amino acids are less sterically hindered than their proline-derived counterparts; this can be critical, especially when sterically demanding carbonyl compounds are utilized in the reaction. Asymmetric catalysis relies on the employment of chiral catalysts;


potential interactions
readily available, versatile in structural variation
enamine derived from primary amino acids
less hindered enamine intermediate

Scheme 3.2 Enamine intermediates derived from primary amino acids.

the wide variety of chiral scaffolds introduced by primary amino acids make them favorable choices in asymmetric synthesis. It is thus not surprising that primary amino acid catalysts quickly caught up and found wide applications in asymmetric organic catalysis in the past few years.

The non-proline amino acid catalysts that will be discussed in this chapter are classified into the following categories (Figure 3.1).

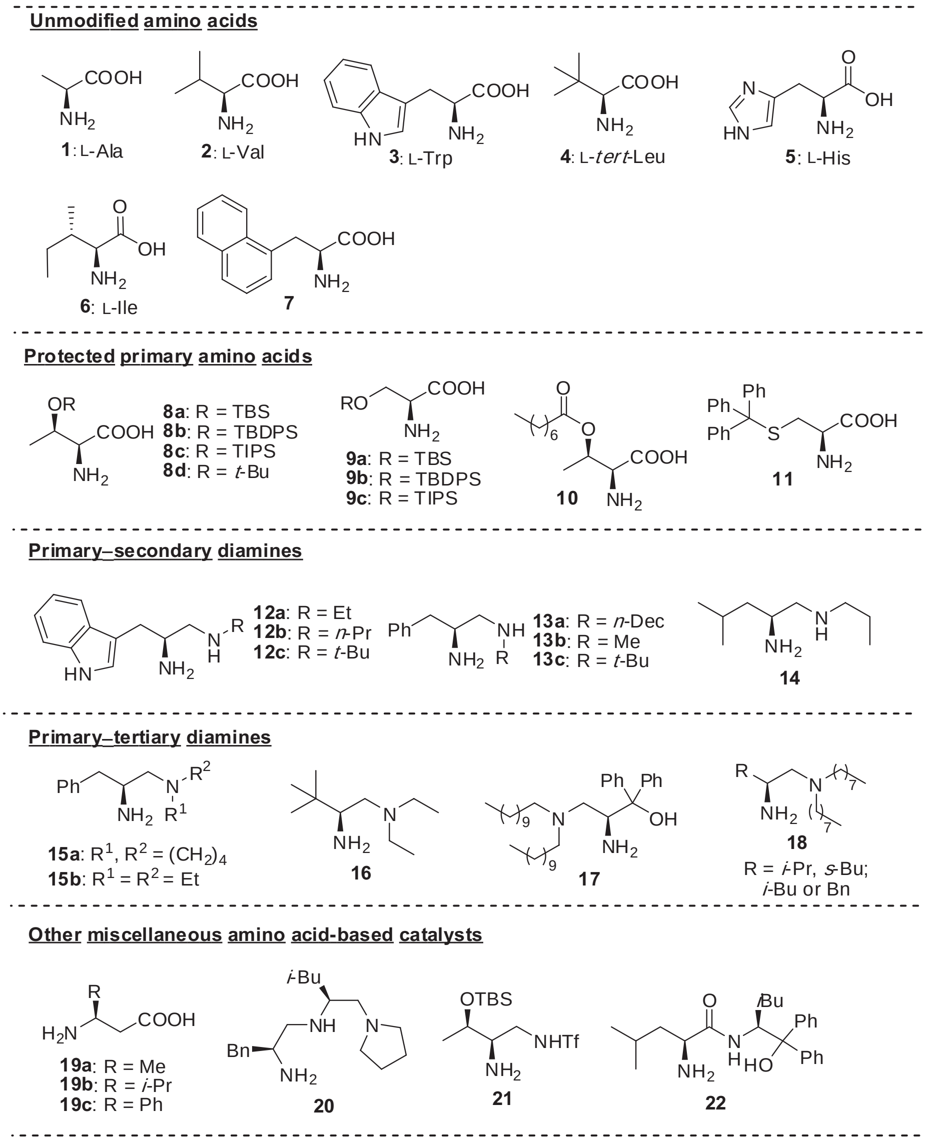


Figure 3.1 Non-proline amino acid catalysts.

3.3.1
Unmodified Amino Acids

Several unmodified amino acids (**1–7**) have been used directly for the activation of substrates via the enamine mechanism. In such transformations, the chirality of amino acids induces stereoselectivity in the product formation. If a high level of enantioselectivity is attainable, such unmodified amino acid catalysts are certainly ideal due to their ready availability and economical nature.

3.3.2
Protected Primary Amino Acids

This type of catalyst is created by simply introducing protection to the functional group at the side chain of amino acids (**8–11**). In particular, a L-threonine core has been shown to be extremely powerful in asymmetric induction. Hydrophobic protective groups were often introduced, and it is believed that hydrophobic effects might play important roles for reactions performed in aqueous medium.

3.3.3
Primary Amino Acid-Derived Diamine Catalysts

Quite recently, chiral diamines have been recognized as effective catalysts in asymmetric catalysis [16]. Utilizing primary amino acid structural scaffolds, several novel diamine catalysts have been developed, which can be classified as primary–secondary diamines (**12–14**) and primary–tertiary diamines (**15–18**). Notably, such diamines are often used in combination with Brønsted acid additives for effective activation of substrates.

For catalysis mediated by primary–secondary diamines, it is believed that the primary amine moiety activates the electrophiles via the formation of iminium intermediates, and the secondary amino group forms a hydrogen bond with the nucleophiles and contributes to their activation. Primary–secondary diamines were found to be useful for a range of reactions, including Michael addition, epoxidation, and Friedel–Crafts alkylation. In primary–tertiary diamine-based catalysis, the general perception is that primary amino group activates the carbonyl substrates via enamine formation, and the hydrogen bonding interactions between tertiary amine-derived ammonium ion and acceptors contribute significantly to the stereochemical control. This type of catalysts was mainly used for aldol reactions.

3.3.4
Other Primary Amino Acid Catalysts

Some other catalysts based on primary amino acid structures, such as β-amino acids, dipeptides, and primary amine–amides/sulfonamides (**19–22**), have also been applied to asymmetric synthesis.

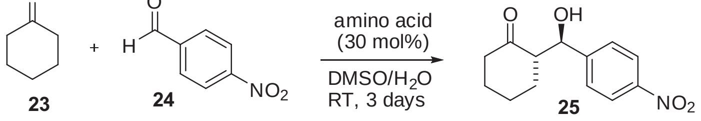
3.4
Applications of Non-Proline Primary Amino Acid Catalysts

In the following sections, applications of the above non-proline amino acid catalysts in asymmetric organocatalytic reactions will be described in detail; the discussion is organized according to the reaction type.

3.4.1
Aldol Reaction

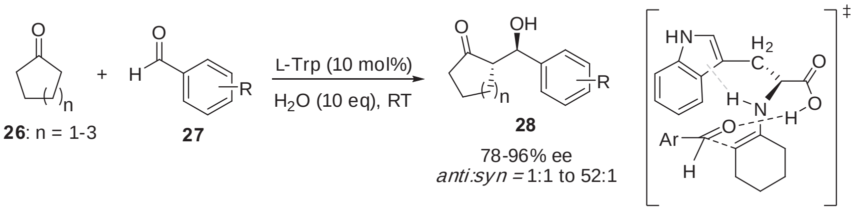
The aldol reaction is one of the oldest and most important methods for the construction of carbon–carbon bonds in organic chemistry [17], and numerous organocatalytic reactions target this important transformation.

In a study on the roles that amino acids might have played in the origin of homochirality, Pizzarello and Weber [18] discovered that primary amino acids, such as alanine and isovaline, catalyzed the aldol reaction of glycoaldehyde in water to generate tetroses. Although the enantioselectivity of the reported reaction was low, it marked the beginning of widespread applications of primary amino acids in the aldol condensation. In 2005, Córdova *et al.* [19] disclosed that natural amino acids, such as alanine and valine, were remarkably effective in promoting direct asymmetric aldol reactions between aromatic aldehydes and cyclic ketones, affording the desired β-hydroxy ketones in high yields and with very high ee. Acyclic ketones could also be used, but only moderate enantioselectivity was attainable (Scheme 3.3). The first utilization of L-tryptophan for the direct intermolecular reaction in aqueous media was reported by the Lu group [20]. In the presence of 10 mol% L-tryptophan, the desired aldol products were obtained with up to 96% ee. Subsequent DFT calculations revealed that N–H/π interaction between the amine N–H and the indole moiety, and the weak N–H…O hydrogen bond between the amino proton and carboxyl oxygen contribute to the lowest-lying transition state. The hydrogen bonding interaction between carboxylic acid OH group and the aldehyde oxygen directs the substrate (Scheme 3.4). Very recently, Itoh and coworkers applied L-*tert*-leucine for the direct aldol reaction of cyclic ketones with aromatic aldehydes. The reaction worked well for cyclohexanone, but was less favorable for pentanone, cycloheptanone, and cyclooctanone [21].



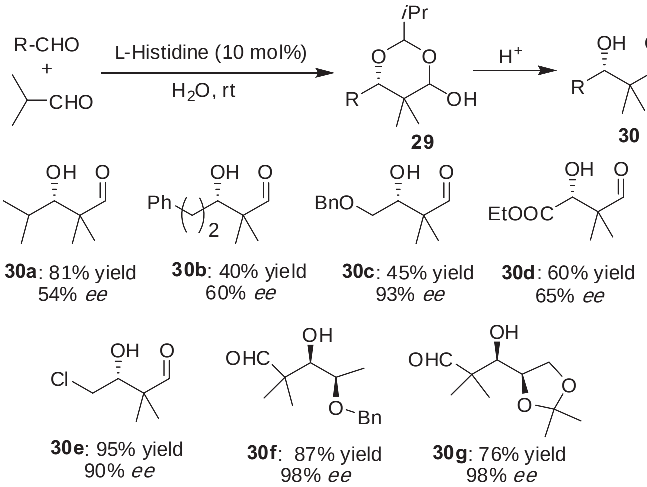
L-Alanine: 95% yield, 15:1 dr, 99% ee; L-Valine: 98% yield, 37:1 dr, >99% ee

Scheme 3.3 Direct aldol reaction catalyzed by simple primary amino acids.



Scheme 3.4 Direct aqueous intermolecular aldol reaction catalyzed by L-tryptophan.

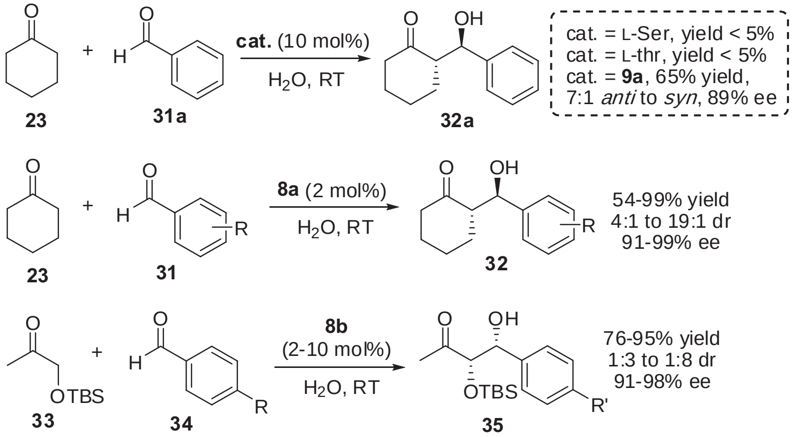
Histidine was found to be an efficient organocatalyst for the intramolecular aldol reaction between different ketone moieties [22]. In 2009, Mahrwald *et al.* [23] reported that histidine could promote intermolecular cross-aldol reactions of enolizable aldehydes (Scheme 3.5). This transformation was promoted by 10 mol% of histidine in water. Very recently, the same group described a general extension of this transformation, and provided deeper mechanistic insights [24]. In contrast to the common *anti*-selectivity in proline catalysis, the aldol adducts with good 2,3-*syn*-diastereoselectivity were observed, which may be attributed to the presence of two possible hydrogen bond donors in histidine. Quantum mechanical calculations were performed to elucidate the origin of the diastereo- and enantioselectivities of the histidine-catalyzed aldol reaction between aldehydes [25]. The computational studies suggest that both the imidazolium and the carboxylic acid functionalities of histidine can stabilize the aldol addition through hydrogen bonding interactions in a Zimmerman–Traxler type [26] transition state. The stereoselectivity was proposed to arise from the minimization of gauche interactions around the C–C bond formed. Very recently, Mahrwald *et al.* disclosed an



Scheme 3.5 Histidine-catalyzed cross aldol reaction of aliphatic aldehydes.

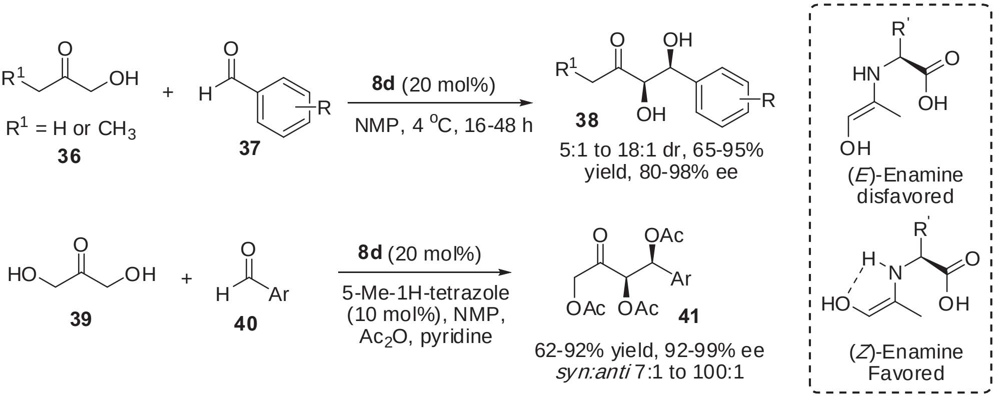
isoleucine (**6**)-catalyzed direct aldol reaction between enolizable aldehydes [27], which complements both proline- and histidine-catalyzed aldol reactions for the aldehyde substrates.

L-Threonine-derived catalysts were demonstrated to be remarkably effective for the direct aldol reaction. Lu *et al.* investigated the potential of serine and threonine analogs in the direct asymmetric aldol reaction in aqueous medium [28]. While L-serine and L-threonine were found to be ineffective, silylated threonine and serine derivatives were wonderful catalysts for the direct aldol reaction of cyclohexanone and aromatic aldehydes in the presence of water, affording the aldol adducts in excellent yields and with nearly perfect enantioselectivities. L-Serine-derived **9a** was inferior to the corresponding threonine-based catalysts. The reaction could be extended to hydroxyacetone, and *syn*-diols were obtained with very good enantioselectivities (Scheme 3.6). Subsequently, Teo and coworkers also employed silylated serine catalysts for the same reaction [29]. Very recently, Córdova *et al.* [30] reported a co-catalyst system consisting of **8a** and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea, and applied such catalytic pairs to the direct aldol reaction between ketones and aromatic aldehydes; both cyclic and acyclic ketones were found to be suitable substrates.



Scheme 3.6 Protected L-threonine or L-serine for the direct aldol reaction.

The Barbas group independently investigated the utilization of protected threonine in the direct aldol reaction [31]. *O*-Bu^t-L-threonine was demonstrated to be an excellent catalyst for the direct aldol reaction of hydroxyacetone and aromatic aldehydes, and the *syn*- aldol products were obtained with good diastereoselectivities and high enantioselectivities. It was proposed that (*Z*)-enamine formation was favored due to the hydrogen bonding interaction of enamine NH and the OH group (Scheme 3.7). The same research group later extended their



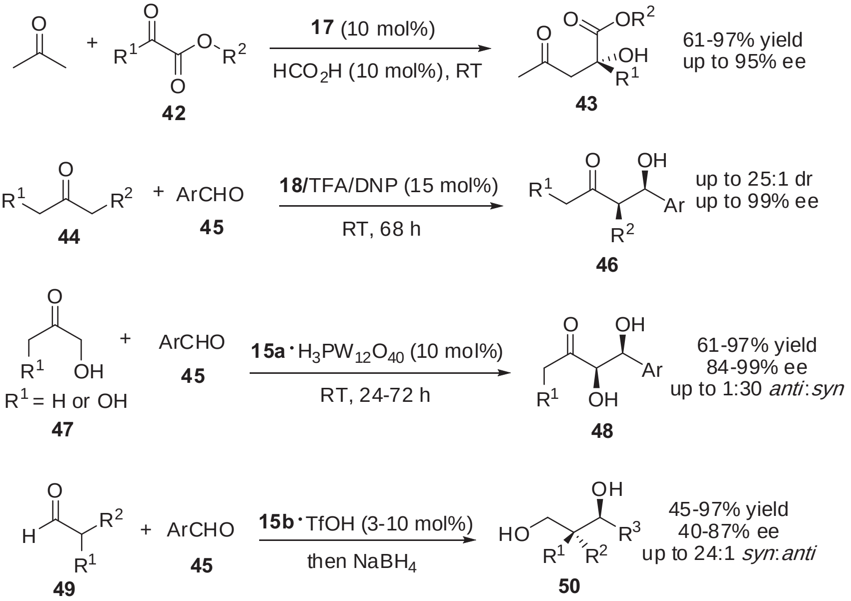
Scheme 3.7 Direct aldol reaction promoted by O-Bu^t-L-threonine.

method to the synthesis of carbohydrates and discovered that DMF/5-methyl-1*H*-tetrazole was an optimal solvent/acid additive combination in promoting *O*-Bu^t-L-threonine-mediated aldol reactions between dihydroxyacetone and aromatic aldehydes [32].

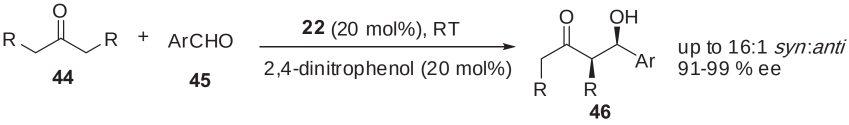
By introducing large acyl groups to the hydroxyl function of threonine, Fu *et al.* developed a series of threonine–surfactant catalysts, and found catalyst **10** was most efficient in promoting highly enantioselective aldol reactions of cyclic ketones and aromatic aldehydes [33].

Amino acid-derived primary–tertiary diamine catalysts have been used extensively in aldol reactions. Lu and Jiang [34] documented a direct asymmetric aldol reaction between acetone and α-ketoesters catalyzed by an L-serine-derived diamine **17.** Sels *et al.* [35] found that several primary amino acid-based diamines (**18**) were efficient catalysts for the *syn*-aldol reaction of linear aliphatic ketones with aromatic aldehydes. Luo and Cheng utilized L-phenylalanine-derived diamine catalyst **15a** for the enantioselective *syn*-aldol reaction of hydroxyl ketones with aromatic aldehydes [36]. Moreover, a highly enantioselective direct cross aldol reaction of alkyl aldehydes and aromatic aldehydes was realized in the presence of **15a** (Scheme 3.8) [37]. Very recently, the same group also achieved a highly enantioselective cross-aldol reaction of acetaldehyde [38]. Da and coworkers [39] discovered that catalyst **22,** in combination with 2,4-dinitrophenol, provided good activation for the direct asymmetric aldol reaction (Scheme 3.9).

Córdova and coworkers demonstrated that simple dipeptides, particularly alanine-containing ones, were effective catalysts for the direct aldol reactions of cyclic ketones with aromatic aldehydes, and the reactions have been explored using either DMSO or water as the reaction medium [40a,b]. Tsogoeva and Wei showed that L-histidine-based dipeptides are good catalysts for the direct aldol reaction of acetone with aromatic aldehydes [41].



Scheme 3.8 Aldol reactions catalyzed by primary–tertiary diamines.

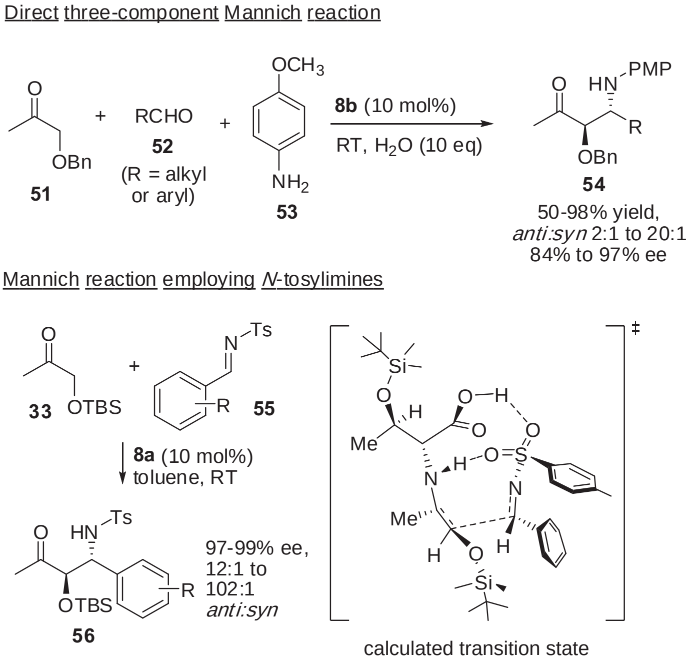


Scheme 3.9 Aldol reactions catalyzed by amino acid-derived amino alcohol.

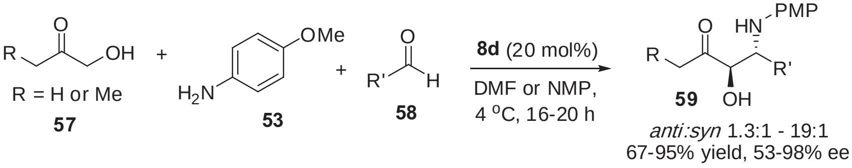
3.4.2
Mannich Reaction

The Mannich reaction is an excellent method for the synthesis of β-amino carbonyl compounds and their derivatives, and unmodified primary amino acids were found to be enormously useful for this important reaction. Córdova *et al.* [42] reported the first primary amino acid-promoted three-component Mannich reaction of ketone, *p*-anisidine, and aldehydes; primary amino acids, such as L-alanine and L-valine, were excellent catalysts and led to the formation of Mannich products with up to >99% ee. Barbas and coworkers [31] also showed L-tryptophan catalyzed the direct three-component Mannich reaction of hydroxyacetone, *p*-anisidine, and aromatic aldehydes; good yields, high diastereoselectivity, and excellent *ee* were attainable.

L-Threonine-derived catalysts were also found to be useful in direct asymmetric Mannich reactions. Lu and coworkers [43] demonstrated that *O*-silylated threonine catalysts were equally effective for the three-component *anti*-selective Mannich reaction of *O*-benzyl hydroxyacetone, *p*-anisidine, and aromatic or aliphatic aldehydes, furnishing *anti*-1,2-amino alcohols (**54**) with excellent enantioselectivities. By utilizing *N*-tosylimines (**55**) as an acceptor, the same group later discovered an extremely *anti*-selective Mannich reaction [44]. In the calculated transition state, it was revealed that both oxygen atoms of the sulfone group were engaged in hydrogen bonding interactions with hydrogens from the NH and carboxylic acid groups (Scheme 3.10). Barbas and coworkers also independently developed a *O*-Bu^t-L threonine-catalyzed direct three-component Mannich reaction for the synthesis of chiral *anti*-1,2-amino alcohols (Scheme 3.11) [31].

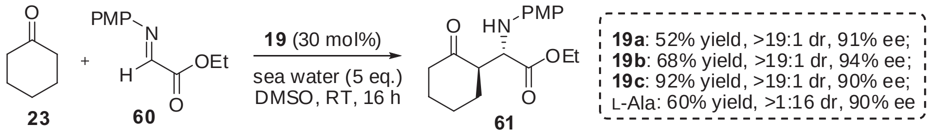


Scheme 3.10 Direct Mannich reactions promoted by protected threonine catalysts.



Scheme 3.11 *O*-Bu^t-L-threonine-catalyzed direct three-component Mannich reaction.

Córdova and Dziedzic [45] examined the catalytic effects of primary β-amino acids in the direct Mannich-type reaction in sea water. Highly *anti*-selective Mannich products were obtained with excellent enantiomeric excesses, and the diastereoselectivity of the reaction was opposite to that of L-alanine-catalyzed reaction (Scheme 3.12).

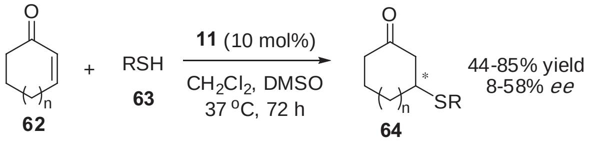


19a: 52% yield, >19:1 dr, 91% ee;
19b: 68% yield, >19:1 dr, 94% ee;
19c: 92% yield, >19:1 dr, 90% ee;
L-Ala: 60% yield, >1:16 dr, 90% ee

Scheme 3.12 β-Amino acid-catalyzed aldol reaction.

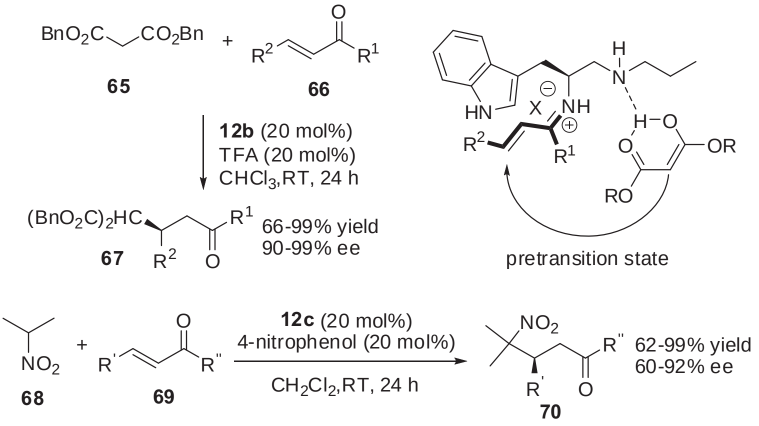
3.4.3
Michael Addition

The Michael addition is one of the most important carbon–carbon bond-forming reactions in organic synthesis [46]. Recently, Yoshida *et al.* [47] examined several primary amino acids in the Michael addition of benzyl thiols to 2-cyclohexe-1-one, and discovered that *S*-triphenylmethyl L-cysteine **11** was the best catalyst for this thio-Michael reaction (Scheme 3.13).

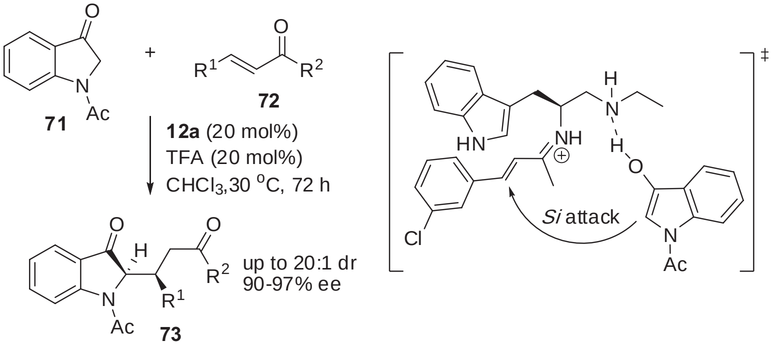


Scheme 3.13 Thio-Michael addition promoted by a primary amino acid.

In 2008, Zhao and coworkers reported an organocatalytic enantioselective Michael addition of malonates to enones catalyzed by amino-acid derived primary–secondary diamines [48a]. A bifunctional iminium mechanism was proposed, in which primary amine is believed to be responsible for the iminium formation with the enone substrates, while the secondary amine activates the malonate **65** (Scheme 3.14). Utilizing a similar strategy, the same group further extended the reaction to include nitroalkanes as a donor in the Michael reaction [48b]. Cordova *et al.* also showed that dipeptide catalysts could promote enantioselective addition of ketones to nitroolefins [49]. Employing diamine catalyst **13a**, Wang *et al.* developed a water-compatible iminium activation for an enantioselective Michael addition of malonates to enones [50a]. Shortly afterwards, the Wang group extended the utility of primary–secondary diamine catalysis to an efficient synthesis of 2-substituted indolin-3-ones [50b]. In the presence of diamine **12a**, indolin-3-one was an effective donor for the conjugate addition to enones; good yields, moderate to high diastereoselectivities, and excellent enantioselectivities were attainable (Scheme 3.15).

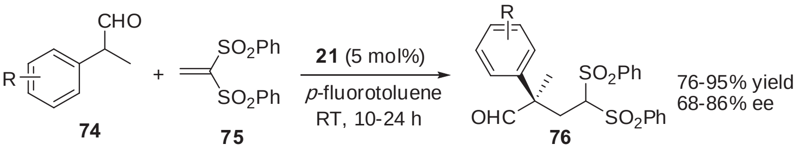


Scheme 3.14 Primary–secondary diamine-promoted Michael additions.



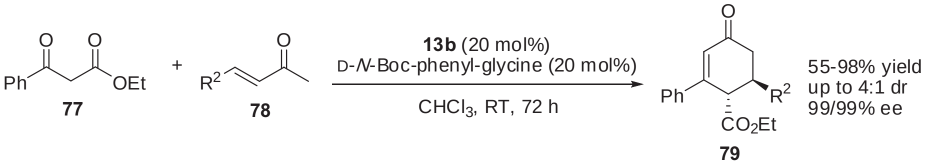
Scheme 3.15 Creation of 2-substituted indolin-3-ones.

Conversion of the carboxylic acid function of amino acids into other hydrogen-bond donating groups generates new catalysts, and their catalytic reactivity and stereoselectivity are expected to differ from that of the parent amino acids. Lu and Zhu [51] reported that threonine-derived primary amine–sulfonamide **21** effectively promoted asymmetric conjugate addition of α,α-disubstituted aldehydes to 1,1-bis(benzenesulfonyl)ethylene, affording products with quaternary stereogenic centers adjacent to an aldehyde group in high yields and good enantioselectivities (Scheme 3.16).



Scheme 3.16 Primary amine–amides/sulfonamide catalysts.

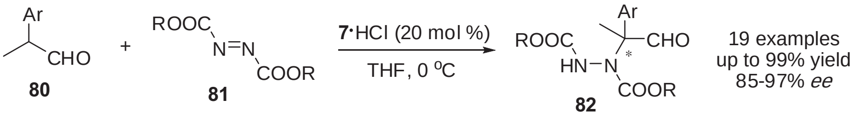
Zhao and coworkers devised enantioselective syntheses of chiral cyclohexenones using primary–secondary diamine-catalyzed cascade reactions (Scheme 3.17). Diamine **13b** promoted a cascade Michael–aldol–dehydration reaction between ketoester **77** and enones **78**, affording highly functionalized chiral cyclohexenones **79** in good yields and with high enantioselectivities, although the diastereoselectivity was poor [52]. The same group also applied a similar approach for an enantioselective synthesis of fluorinated cyclohexenones via Robinson annulation reaction [53].



Scheme 3.17 Synthesis of chiral cyclohexenones via Michael–aldol–dehydration reaction.

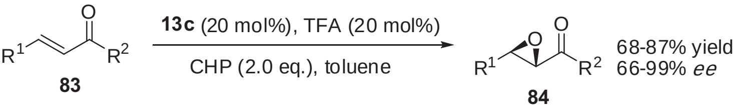
3.4.4
Other Reactions

By employing simple primary amino acids, Xu and Wang achieved an enantioselective α-amination of branched aldehydes [54]. 3-(1-Naphthyl)alanine hydrochloride **7** was found to be the best catalyst, furnishing the desired amination products in moderate to excellent yields and very good enantioselectivities (Scheme 3.18).



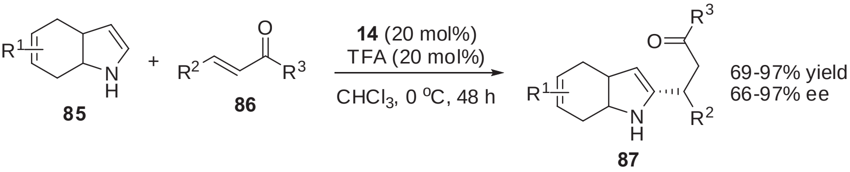
Scheme 3.18 Amination reaction of branched aldehydes.

The Zhao group recently disclosed an enantioselective epoxidation of α,β-unsaturated ketones promoted by primary–secondary diamine catalyst **13c**; the corresponding epoxides were obtained with excellent enantioselectivities (Scheme 3.19) [55].



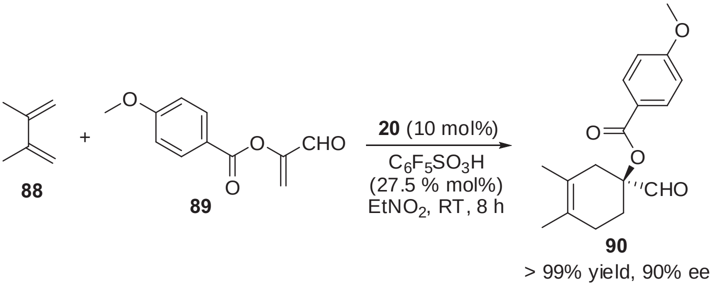
Scheme 3.19 Primary–secondary diamine-catalyzed epoxidation.

Primary–secondary diamine catalyst **14** was found to be useful in the Friedel–Crafts alkylation reaction (Scheme 3.20). In the presence of **14**/trifluoroacetic acid (TFA), alkylation of 4,7-dihydroindoles **85** with α,β-unsaturated enones **86** proceeded well, and the desired alkylation products were obtained in high yields and with excellent enantioselectivities [56].



Scheme 3.20 Diamine-promoted Friedel–Crafts alkylation.

Ishihara has designed dipeptide-derived triamine catalyst **20** and elegantly demonstrated its value in a Diels–Alder reaction [57]. The primary amine group, in combination with an acid co-catalyst, facilitated the activation of α-acyloxyacrolein in the Diels–Alder reactions, and the adducts were obtained in good yields and with good to excellent enantioselectivities (Scheme 3.21).



Scheme 3.21 Diels–Alder reaction catalyzed by triamine **20**.

3.5
Conclusions

This chapter provides a snapshot of recent impressive advances in non-proline amino acid catalysis. A good range of enantioselective processes were realized by utilizing primary amino acid catalysts, and such methods represent powerful and versatile synthetic tools for organic chemists. Amino acid-based catalysts are now well-recognized and considered as privileged catalysts, since they are readily available and economical, and they are also powerful and versatile in asymmetric induction for various important organic transformations. The remarkable applicability of primary amino acid catalysts in asymmetric catalysis demonstrates the amazing power of amino acid structural motifs in stereochemical control. It is anticipated that many more powerful and novel catalytic systems built upon chiral elements of simple amino acids are to come in the future, thus greatly advancing the field of asymmetric synthesis and catalysis.

Acknowledgments

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4

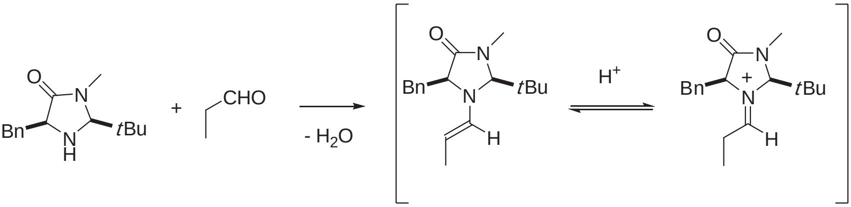
Chiral Imidazolidinone (MacMillan's) Catalyst

Rainer Mahrwald

4.1

Introduction

Chiral imidazolidin-4-ones – chiral secondary amines – had already been successfully used in asymmetric synthesis before they started their own career as organocatalysts [1]. They were deployed as chiral auxiliaries for alkylation processes [2], Michael additions [3], and aldol reactions [4]. For syntheses of this class of catalyst see Reference [5]. The ability to activate both carbonyl compounds by enamine formation as well α,β-unsaturated carbonyl compounds by intermediate formation of iminium ions makes imidazolidin-4-ones a valuable class of organocatalysts in both series. Thus, they can roughly be divided by their mode of activation into enamine [6] or iminium [7] catalysis (Scheme 4.1). These catalysts were successfully deployed in a wide range of several important enantioselective C–C bond formation and functionalization processes. Figure 4.1 shows the chiral imidazolidinones covered in this chapter.



Scheme 4.1 Enamine and imine catalysis.

4.2

Enamine Catalysis

Chiral imidazolidin-4-ones operate as chiral secondary amines to activate aldehydes by enamine formation. Enamines of imidazolidin-4-one and hydrocinnamaldehyde

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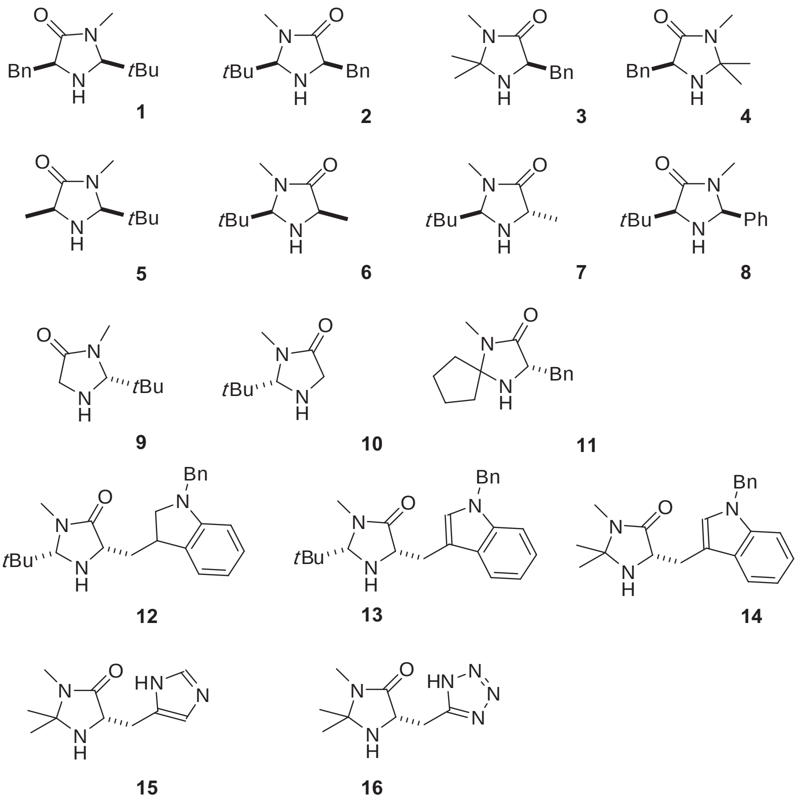


Figure 4.1 Chiral imidazolidinones covered in this chapter.

are stable and were detected by NMR experiments [8]. This fact was utilized by several groups to enantioselectively functionalize aldehydes at the α-position. In 2004 the first enantioselective α-chlorination in the presence of catalytic amounts of imidazolidinone was described by MacMillan *et al.* [9]. In particular, the introduction of fluorine is of considerable interest since fluorine-substituted bioactive compounds are metabolically stable and are detectors of hydrogen bonding capacity. In 2005 MacMillan and Beeson [10a] reported studies on the direct asymmetric α-fluorination of aldehydes using *N*-fluorobenzenesulfonimide (NFSI) as the source of electrophilic fluorine. Scheme 4.2 depicts the results of these investigations. In addition, the successful application of this method for the fluorination of pregnanedione and cholestanone was described by the authors [11].

For the synthesis of chiral α-fluoroamines via asymmetric fluorination of aldehydes see Reference [12]. Finally, this method was also used for the synthesis of α-fluorinated capsaicin [13] and an agonist of the GPR119 receptor [14].

By deployment of lithium chloride or sodium chloride – as a source of chlorine – α-chlorinated enolizable aldehydes are accessible in the presence of a Ce(IV)

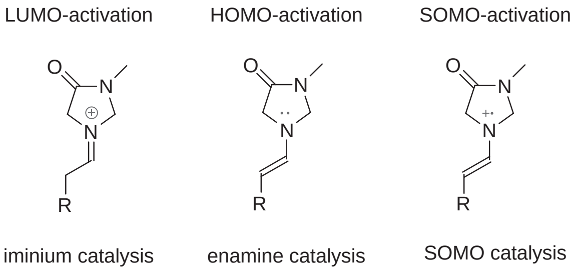
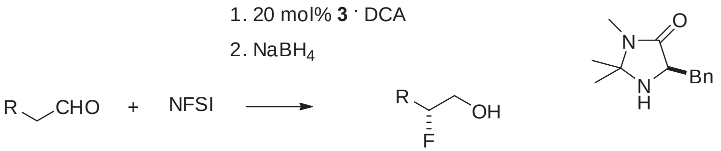


Figure 4.2 Comparison of SOMO catalysis with iminium and enamine catalysis.



17a-d

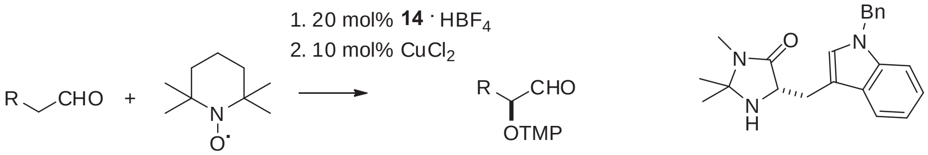
3

17a: R=$n\text{C}_9\text{H}_{19}$, 70%, 94% ee
17b: R=Ph: 54%, 99% ee
17c: R=Cy: 96%, 99% ee
17d: R=Bn: 71%, 96% ee

Scheme 4.2 Asymmetric α-fluorination of aldehydes; DCA: dichloroacetic acid.

oxidant (SOMO catalysis, see Figure 4.2). However, rapid racemization is observed during this process, depending on reaction temperature. An intermediate enamine–iminium equilibrium is suspected. This problem can be overcome by deployment of a catalyst, which is inert to enamine formation with the α-chloro aldehyde. For this procedure, imidazolidinone **7** was used in the presence of the oxidant combination of copper(II) salts and sodium persulfate. Under these reactions conditions α-chlorinated aldehydes were obtained at room temperature with high levels of yields as well as enantioselectivities [15]. This protocol was applied in the total synthesis of ripostatin B [16], (+)-goniothalesdiol [17], and (−)-*trans*-aerangis lactone [18].

In 2007 Sibi and Hasegawa reported an asymmetric radical α-oxygenation reaction by TEMPO (2,2,6,6-tetramethylpiperidinoxyl) using chiral imidazolidin-4-ones as organocatalysts [19]. These transformations were carried out in the presence of catalytic amounts of $FeCl_3$ and co-oxidant ($NaNO_2/O_2$). Later mechanistic studies in this field by the MacMillan group revealed an enamine activation and catalysis during this transformation. An activation of TEMPO by metal complexation is assumed, which makes utilization of the co-oxidant-system $NaNO_2/O_2$ unnecessary (Scheme 4.3) [20].

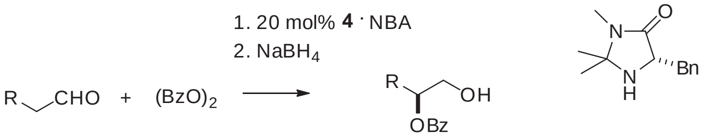


18a: R=nC$_6$H$_{13}$: 86%, 90% ee
18b: R=iPr: 88%, 94% ee
18c: R=Bn: 89%, 92% ee

14

Scheme 4.3 Enantioselective α-oxidation of aldehydes.

By treatment of enolizable aldehydes with benzoyl peroxide in the presence of catalytic amounts of chiral imidazolidin-4-one **4** gives direct access to enantioenriched α-oxybenzoylated aldehydes (Scheme 4.4) [21]. The α-oxygenated aldehydes were isolated as their primary alcohols **19a–d** to aid in analysis.



19a: R=nPr: 72%, 93% ee
19b: R=iPr: 40%, 93% ee
19c: R=Me: 50%, 93% ee
19d: R=Bn: 42%, 60% ee

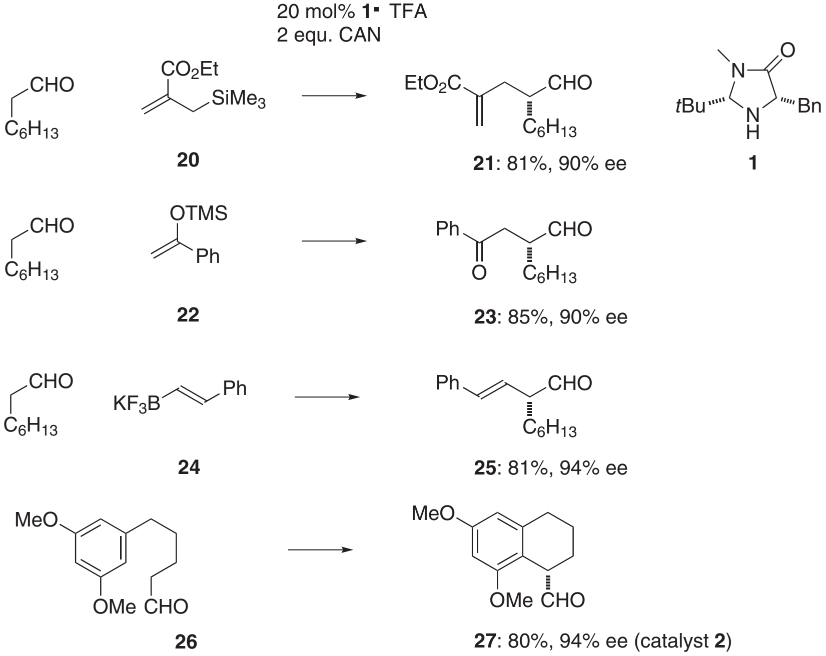
4

Scheme 4.4 α-Oxybenzoylation of aldehydes. NBA: *p*-nitrobenzoic acid.

For an example of an α-selenenylation of enolizable aldehydes in the presence of polystyrene-supported imidazolidin-4-ones see Reference [22]. Dixon and coworkers described an aryloxylation process of aldehydes using an inverse electron demand hetero-Diels–Alder reaction of *in situ* generated enamines and *o*-quinone [23]. Enantioenriched α-oxygenated products were isolated with good yields.

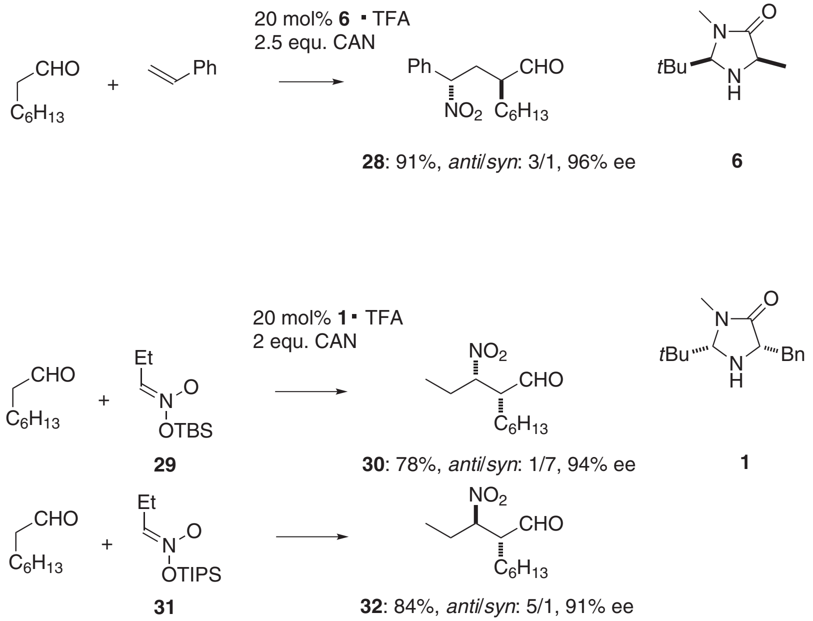
The ability of enamines to form *in situ* generated radicals gives rise to an entirely new principle of activation and thus to a series of very useful and highly selective previously unknown C–C bond formation processes. Thus, enamine catalysis changed into SOMO-catalysis (SOMO – singly occupied molecular orbital) (Figure 4.2) [24]. For direct experimental evidence of an enamine radical cation in SOMO catalysis see Reference [25]. These types of transformations were extensively elaborated by the MacMillan group. The first steps in this new concept were accomplished by the formation of radicals of enamines of imidazolidin-4-ones.

The generation of enamine radicals was realized by oxidation with ceric ammonium nitrate (CAN). MacMillan *et al.* have demonstrated the usefulness of this concept with a series of reaction protocols. Successful examples for this SOMO activation were reported for intermolecular [26] as well as intramolecular α-allylation [27], α-vinylation [28], α-enolation [29], and intramolecular α-arylation [30] of enolizable aldehydes. These transformations are each illustrated with a representative example (allylation → **21**, enolation → **23**, vinylation → **25**, arylation → **27**, Scheme 4.5).



Scheme 4.5 SOMO activation.

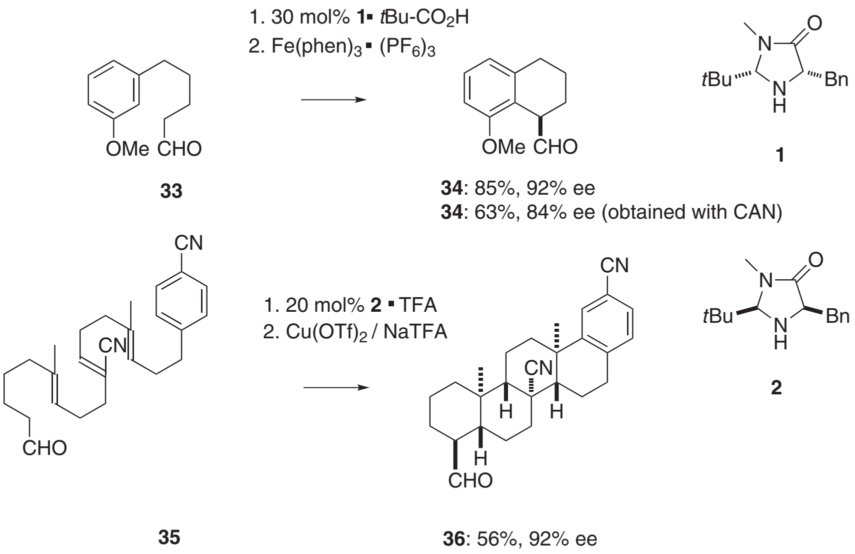
In general, stereogenic centers were created with extremely high degrees of enantioselectivities. Enantioselective vinylation was carried out with the corresponding vinyl potassium trifluoroborate salt. When used with styrene in these transformations an additional oxidation accompanies the C–C bond formation process [31]. As a result, the corresponding γ-nitrates were isolated with high degrees of enantioselectivities (**28**, Scheme 4.6). An *anti*-diastereoselectivity of about 3 : 1 was detected. The corresponding β-enantioenriched nitrates are accessible by asymmetric α-nitroalkylation of enolizable aldehydes. In these transformations silylated nitronates were reacted under standard SOMO conditions. Interestingly, the diastereoselectivity can be controlled by the nature of silyl group of nitronates deployed (TBS → *syn*-**30**; TIPS → *anti*-**32**, Scheme 4.6) [32].



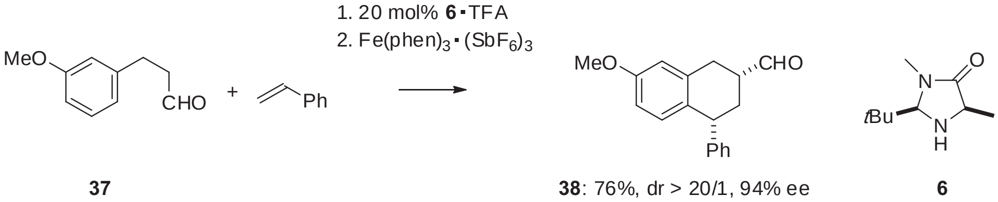
Scheme 4.6 Asymmetric β- and γ-nitroalkylation of aldehydes.

At nearly the same time MacMillan and coworkers developed a new protocol for SOMO-catalyzed intramolecular arylation of enolizable aldehydes (Scheme 4.7) [33]. In these studies the required oxidation step was accomplished by tris-phenanthroline complexes of iron(III) bearing non-nucleophilic counterions, such as $\mathrm{Fe(phen)_3 \cdot (PF_6)_3}$. Higher degrees of enantioselectivities were obtained compared to oxidations with CAN (see **34**, Scheme 4.7). Using this method a simple three-step-access to (–)-tashiromine was elaborated by the authors. For theoretical calculations of this transformation see Reference [34]. By extension of this concept to suitable requisite tethered polyenes the authors were able to establish a powerful cascade reaction leading to defined configured polycyclic structures (**36**, Scheme 4.7). The oxidation step in this process was achieved by slow addition of $\mathrm{Cu(OTf)_2}$/TFA sodium salt [35].

A similar intermolecular version of these radical-mediated cyclizations can be achieved by deployment of suitable γ-substituted enolizable aldehydes in reactions with styrenes. It is assumed that an intermediary formed enamine radical of the organocatalyst and the aldehyde enantioselectively react with styrene to give an iminium ion. These intermediately alkylated radicals cyclize under oxidative conditions to give carbocycles (e.g., **38** in Scheme 4.8). In the end these transformations represent formal cycloadditions under oxidative conditions. Thus, a series of highly substituted and defined configured six- and five-membered carbocycles are accessible with high degrees of stereoselectivities [36].

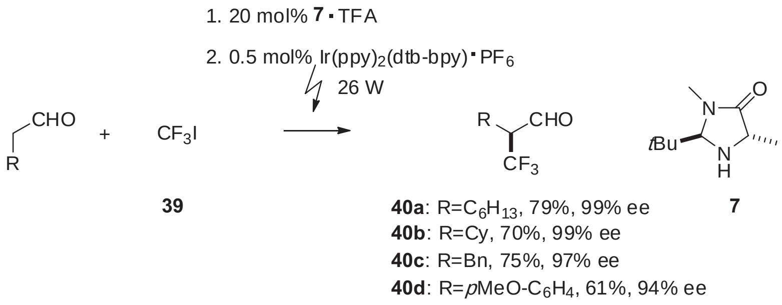


Scheme 4.7 SOMO-catalyzed intramolecular α-arylation of aldehydes.



Scheme 4.8 SOMO-catalyzed intermolecular cyclization.

The radicals of alkylating agents also react with enamines of chiral imidazolidin-4-ones and enolizable aldehydes in the sense of an α-alkylation reaction. This was again demonstrated by the MacMillan group. Radicals of suitable bromo or iodo compounds can be generated by means of photoredox catalysis. These radicals react with enolizable aldehydes to give α-alkylated aldehydes with high degrees of enantioselectivity. Thus direct α-alkylations of aldehydes with α-bromocarbonyl compounds in the presence of ruthenium photocatalysts and fluorescent light can be achieved [37]. When used with benzyl bromide, these reactions were carried out in the presence of iridium complexes and in the presence of household light [38]. Scheme 4.9 gives some results of reactions with trifluoromethyl iodide **39** in the presence of iridium complexes as the photoredox catalyst [39].



39

40a: R=C_6H_{13}, 79%, 99% ee

40b: R=Cy, 70%, 99% ee

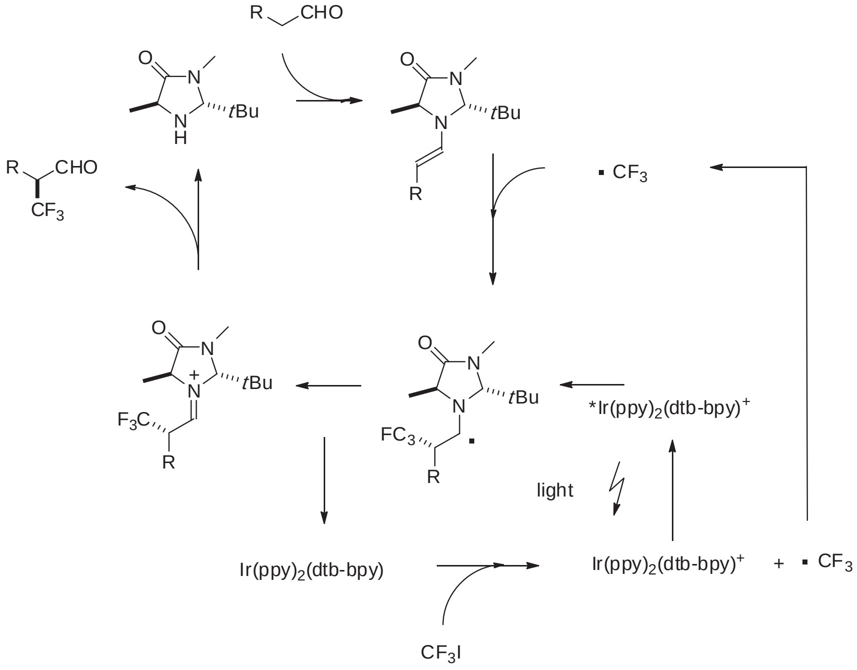
40c: R=Bn, 75%, 97% ee

40d: R=*p*MeO-C_6H_4, 61%, 94% ee

7

Scheme 4.9 Enantioselective α-trifluoromethylation of aldehydes.

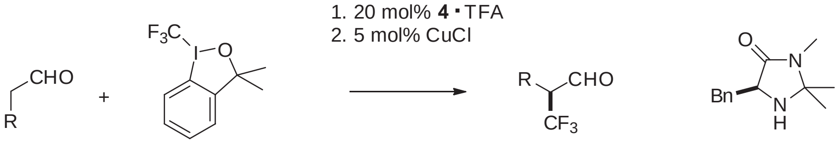
Scheme 4.10 gives an insight into this reaction mechanism. It is supposed that the electron-rich iridium-complex Ir(ppy)$_2$(dtb-bpy) generates the electrophilic trifluoromethyl radical via a single-electron transfer. This trifluoromethyl radical reacts with the enamine of the organocatalyst **7** and enolizable aldehydes highly enantioselectively. The second catalytic cycle, the photoredox cycle, was realized by oxidation/reduction processes of transition metal complexes with the aid of light, as depicted in Scheme 4.10 for the trifluoromethylation of aldehydes.



Scheme 4.10 Proposed reaction mechanism for the trifluoromethylation of aldehydes.

Zeitler *et al.* have developed a metal-free version of such a cooperative organo-photoredox catalysis. They used eosin as a powerful photocatalyst in the asymmetric α-alkylation of enolizable aldehydes. Their results are comparable to those obtained in the transition metal series [40].

Allen and MacMillan demonstrated the introduction of a trifluoromethyl group at the α-position of enolizable aldehydes by a simple deployment of the corresponding iodonium salts [41]. Enamines of enolizable aldehydes and chiral imidazolidin-4-ones react with trifluoromethyl-benziodoxole in the presence of catalytic amounts of Lewis acids to give α-trifluoromethylated aldehydes with high degrees of enantioselectivities (Scheme 4.11).



41a: R=Bn, 81%, 94% ee

41b: R=Cy, 72%, 94% ee

41c: R=CH_2-C_6H_4-OMe, 87%, 96% ee

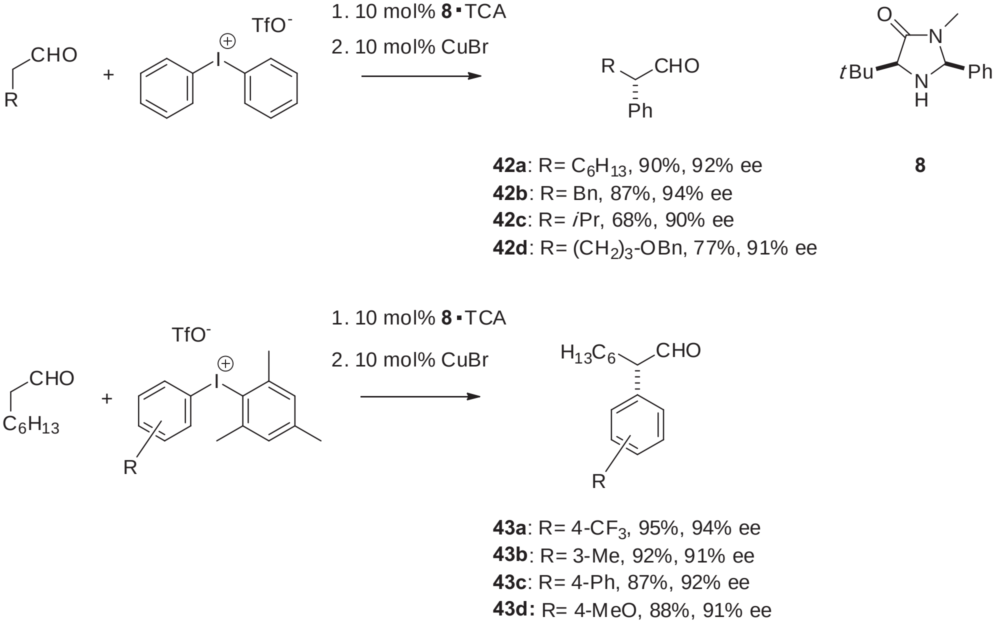
4

Scheme 4.11 Asymmetric α-trifluoromethylation of enolizable aldehydes by organo- and metal catalysis.

When used with diphenyliodonium salts in the presence of a metal and an organocatalyst the enantioselective introduction of a phenyl group at the α-position of aldehydes can be accomplished [42]. This transformation can be extended to a more general concept of enantioselective α-arylation of aldehydes by deployment of different substituted diaryl-iodonium salts. In these reactions CuBr was used as Lewis acid (Scheme 4.12). Based on these findings the authors were able to develop a rapid asymmetric synthesis of the anti-inflammatory drug (*S*)-ketoprofen.

In addition, asymmetric α-alkylation of enolizable aldehydes by diarylmethanols is possible by enamine catalysis. This concept is based on the utilization of stabilized carbocations generated *in situ* from benzylic alcohols. Cozzi and coworkers first realized this concept with the deployment of chiral imidazolindin-4-ones (Scheme 4.13) [43].

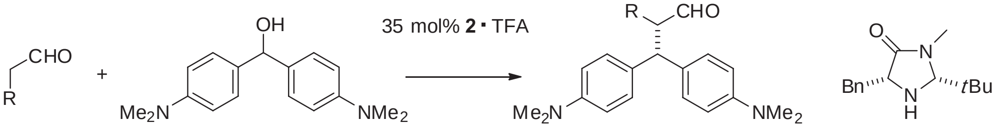
This concept – the organocatalyzed α-alkylation of enolizable aldehydes with stabilized carbocations – has been extended to the deployment of several other substrates and reactions conditions. Oxidation in these processes was achieved by means of equimolar amounts of DDQ (2,3-dichloro-5,6-dicyanobenzoquinone). Selected results of this investigation are depicted in Scheme 4.14 [44]. For a combination of organocatalysis and electrochemistry using these substrates see Reference [45].



42a: R= C_6H_{13}, 90%, 92% ee
42b: R= Bn, 87%, 94% ee
42c: R= *i*Pr, 68%, 90% ee
42d: R= $(CH_2)_3$-OBn, 77%, 91% ee

43a: R= 4-CF_3, 95%, 94% ee
43b: R= 3-Me, 92%, 91% ee
43c: R= 4-Ph, 87%, 92% ee
43d: R= 4-MeO, 88%, 91% ee

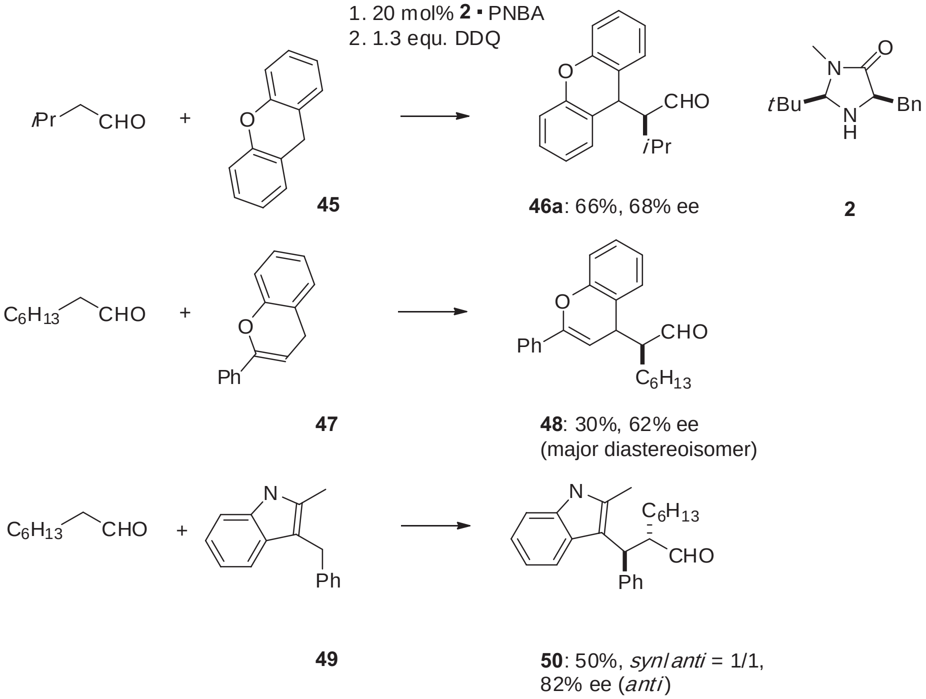
Scheme 4.12 Asymmetric α-arylation of enolizable aldehydes, TCA – trichloroacetic acid.



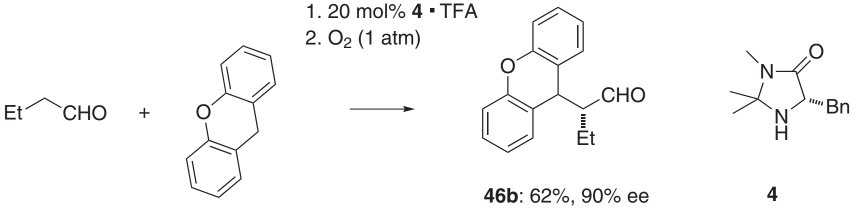
44a: R=Me, 95%, 77% ee
44b: R=*i*Pr, 79%, 69% ee
44c: R=C_6H_{13}, 92%, 78% ee
44d: R=Bn, 77%, 77% ee

Scheme 4.13 Asymmetric α-alkylation of aldehydes.

When used with molecular oxygen as oxidant, an increase in enantioselectivities is observed (compare **46a** in Scheme 4.14 with **46b** in Scheme 4.15). Jiao *et al.* developed a protocol for the successful execution of an asymmetric oxidative α-alkylation of enolizable aldehydes (Scheme 4.15). In addition, the authors have given experimental evidence for the formation of an intermediately peroxide, which produces stabilized carbocations [46].

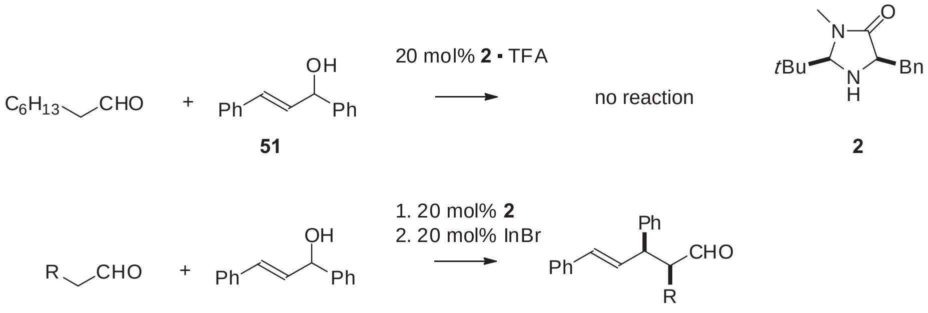


Scheme 4.14 Organocatalytic C–H activation.



Scheme 4.15 Organocatalytic C–H activation.

Several other stabilized carbocations were utilized for asymmetric organocatalyzed transformations. A comparable and similar benzylic situation is given by the utilization of allylic alcohols (Scheme 4.16). These substrates are completely unreactive under organocatalyzed reactions conditions. But, by a combination of metal- and organocatalysis, the same authors were able to realize an enantioselective α-alkylation of enolizable aldehydes with allylic alcohols [47]. The corresponding allylic cations were formed by the use of catalytic amounts of indium salts. Thus, various several different aromatic allylic alcohols were converted into the corresponding aldehydes **52a–c** with high enantioselectivity.



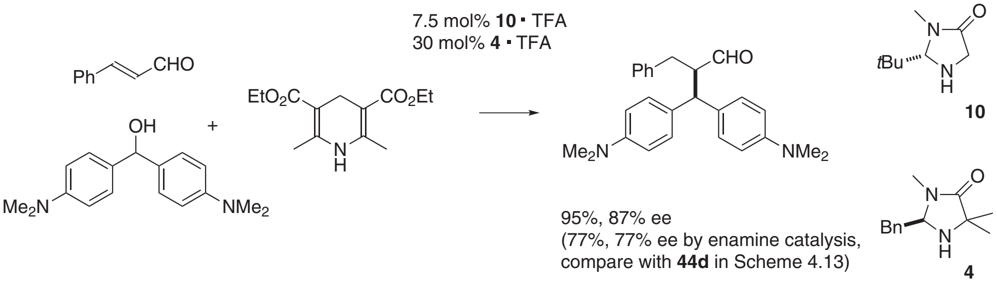
52a: R=C_6H_{13}, 70%, *syn*/*anti*: 2:1, 90% ee (*syn*)
52b: R=Me, 63%, *syn*/*anti*: 2:1, 88% ee (*syn*)
52c: R=Bn, 90%, *syn*/*anti*: 2:1, 89% ee (*syn*)

Scheme 4.16 Merging organo- and metal catalysis.

Very recently, Cozzi *et al.* successfully demonstrated the application of this methodology for the α-alkylation of the formyl group to enolizable aldehydes. This was achieved by a reaction of benzodithiolylium tetrafluoroborate (a stabilized carbenium ion) in the presence of several different substituted imidazolidin-4-ones [48]. After reductive removal of the benzodithiol group access to chiral α-branched primary alcohol is given. Using this method optically pure arundic acid is obtained by a three-step synthesis.

This type of asymmetric α-alkylation of aldehydes was combined with an asymmetric hydride transfer reaction to α,β-unsaturated aldehydes. Thus, when used with iminium and enamine activation, access to α-alkylated aldehydes is given. The yields and enantioselectivities observed are better than those described for the enamine catalysis (Scheme 4.17) [49].

In addition, propargylic alcohols can generate stabilized carbocations under metal- and organocatalysis conditions. Thus, when used with enolizable aldehydes under these reactions, asymmetric access to the corresponding alkylated propargylic compounds is given [50].



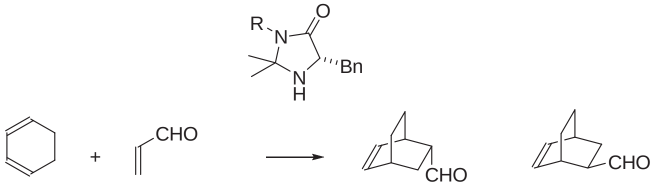
95%, 87% ee
(77%, 77% ee by enamine catalysis, compare with **44d** in Scheme 4.13)

Scheme 4.17 α-Alkylation of aldehydes.

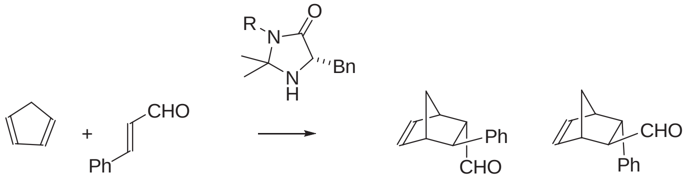
Furthermore, *N*-benzylic sulfonamides can generate stabilized carbocations under conditions of organocatalysis. This was reported for the reactions of ketones and aldehydes in the presence of catalytic amounts of chiral imidazolidin-4-ones [51].

4.3
Iminium Catalysis

The mode of iminium activation of carbonyl compounds is the domain of many and various cycloadditions and conjugate additions. As discussed in the



entry	catalyst	endo	/	exo
1	R: Me	90 (88% ee)		10
2	R: CH_2-C_6H_4-p-$(CH_2)_2$-C_8F_{17}	93 (93% ee)		7 [56]
3	R: Me (montmorillonite entrapped)	96 (92% ee)		4 [57]
4	R: Me (immobilized)	95 (80% ee)		5 [58]
5	R: Me (in ionic liquid: bmim-OTf)	95 (88% ee)		5 [59]

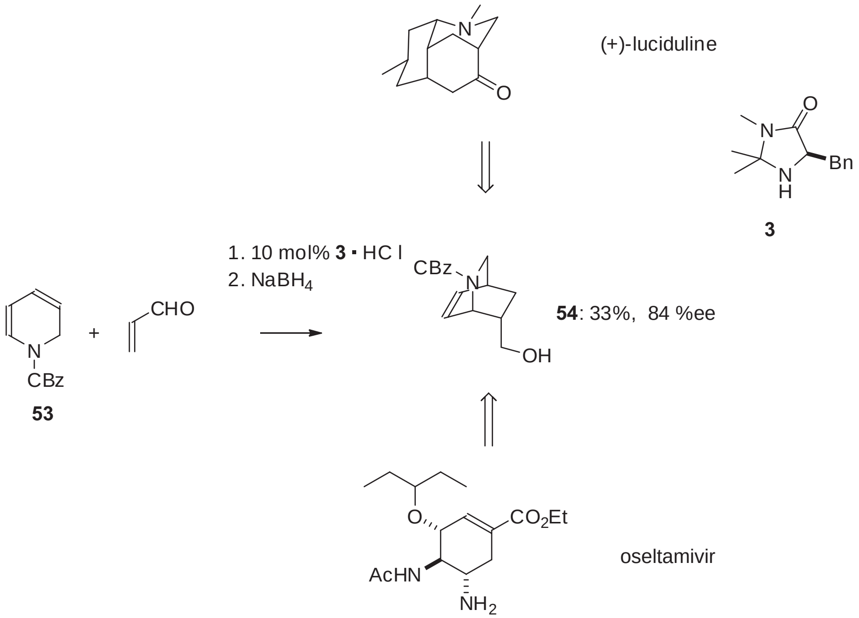


entry	catalyst	endo	/	exo
6	R: CH_2-imidazolyl	55 (60% ee)		45(68% ee) [60]
7	R: CH_2-tetrazolyl	40 (90% ee)		60 (89% ee) [60]
8	R: Me (polymeric sulfonic acid)	45 (92% ee)		55 (88% ee) [61]
9	R: *n*Bu (on mesoporous material)	48 (95% ee)		52 (92% ee) [62]
10	R: Me (on siliceous mmesocellular foam)	44 (74% ee)		56 (73% ee) [63]

Scheme 4.18 Imidazolidinone-catalyzed Diels–Alder reactions.

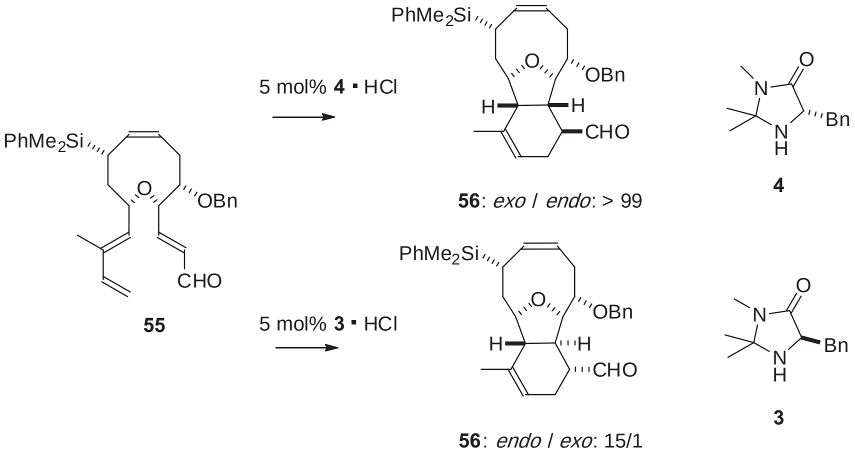
introduction, imidazolidin-4-ones can activate α,β-unsaturated carbonyl compounds by formation of intermediary iminium ions (Scheme 4.1). Stable iminium salts of imidazolidones and cinnamaldehyde were prepared and characterized by X-ray structure analysis [52]. For calculations of the reactivities of iminium ions see Reference [53]. The ability to form iminium salts was utilized in several important C–C bond formation processes, such as Diels–Alder reactions. Numerous publications have appeared [54] since the first organocatalyzed Diels–Alder reaction reported by MacMillan *et al.* in 2000 [55]. Several groups reported improvements and applications of chiral imidazolidin-4-ones under different conditions in these transformations. These results are illustrated by archetypical Diels–Alder reactions of cyclohexadiene and acrolein and cyclopentadiene and cinnamaldehyde (Scheme 4.18).

The influence of solvents [64] and comparisons with catalysts of the diarylprolinol series [65] were reported. For theoretical calculations on stereocontrol see Reference [66]. In addition, imidazolidin-4-one catalyzed cycloadditions have been used in several total syntheses of natural products. Intramolecular Diels–Alder reactions (IMDA) were reported as key steps in the synthesis of bicyclo-undecenes [67], amaminols [68], solanapyrones [69], telomerase inhibitor UCS1025A [70], englerin A [71], (–)-*nor*-platencin [72], and muironolide A [73]. In addition, asymmetric [3+2]-cycloadditions of azomethines were accomplished in the presence of chiral imidazolidinones [74]. Intermolecular cycloadditions of dihydropyridine **53** and acrolein catalyzed by imidazolidin-4-ones were reported. The chiral azabicyclooctenol **54** was isolated as the important key intermediate in the total synthesis of lycopodium alkaloids [75] (e.g., luciduline) and oseltamivir (Scheme 4.19) [76].



Scheme 4.19 Total syntheses of luciduline and oseltamivir.

An instructive example of the stereoselective course of this reaction is given by an intramolecular cycloaddition during the total synthesis of eunicellin [77]. Both enantiomers of an imidazolidin-4-one were deployed in this key step reaction (**4** and **3**, Scheme 4.20).



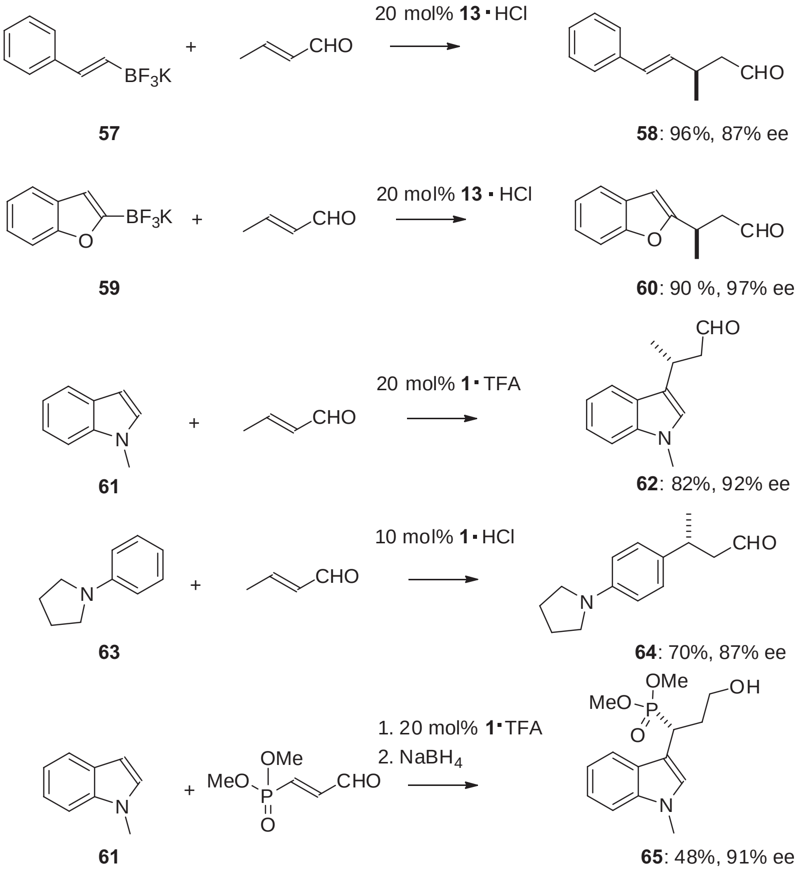
Scheme 4.20 Total synthesis of eunicellin (**56**).

The generation of an iminium ion of α,β-unsaturated carbonyl compounds lowers the LUMO energy. As a result, the α-CH acidity increases as well as the ability to participate in conjugate additions. The first organocatalyzed 1,4-addition to α,β-unsaturated aldehydes was reported by the MacMillan group [78]. For theoretical explorations of the configurative outcome of Michael additions of pyrroles and indoles to crotonaldehyde see Reference [79]. This transformation has been widely used in Friedel–Crafts alkylations of α,β-unsaturated carbonyl compounds (see Reference [1b] and reports cited therein). Comparable examples of this transformation with (*E*)-crotonaldehyde in the intermolecular series were found in aryl alkylation with trifluoroborate (**58** and **60**) [80], indole alkylation (**62**) [81], Friedel–Crafts alkylation of electron-rich benzenes (**64**) [82], and Friedel–Crafts alkylation with phosphonates (**65**) [83] (Scheme 4.21).

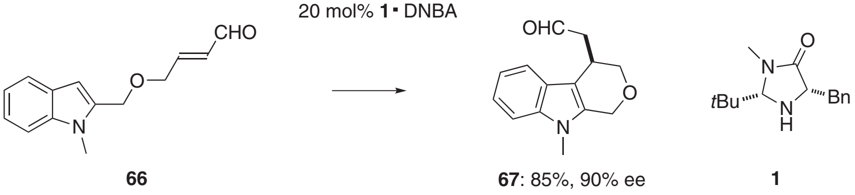
An intramolecular version of this methodology was reported by Xiao *et al.* [84] (Scheme 4.22).

Applications of this methodology were reported in total syntheses of (+)-frondosin B [85], diazonamide A [86], alkaloids [87], (+)-tolterodine [88], (+)-curcuphenol [89], and in pharmaceutical chemistry [90].

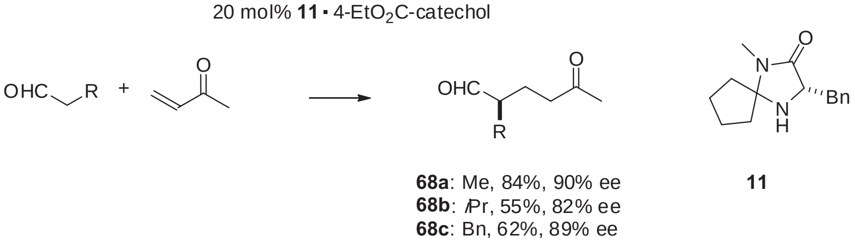
Several other asymmetric inter- as well intramolecular Friedel–Crafts alkylation with α,β-unsaturated aldehydes have been described but without any configurative assignment [91]. Asymmetric carba-Michael additions of aldehydes to enones catalyzed by a chiral imidazolidin-4-one were reported by Gellman *et al.* [8] (Scheme 4.23).



Scheme 4.21 Intermolecular asymmetric conjugate additions.



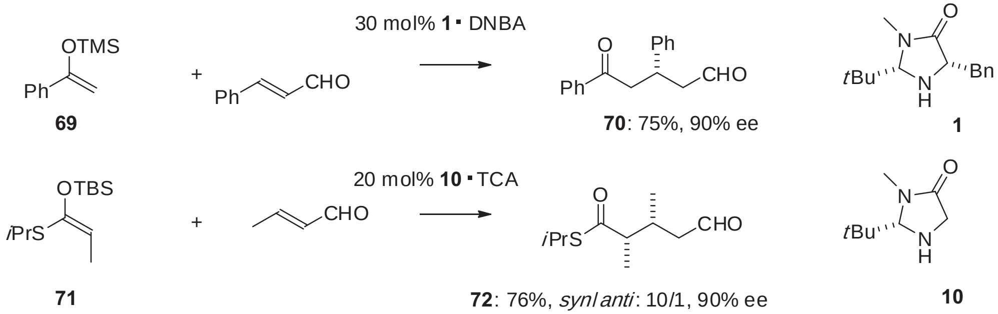
Scheme 4.22 Intramolecular conjugate addition of indoles. DNBA = 3,5-dinitrobenzoic acid.



Scheme 4.23 Carba-Michael addition.

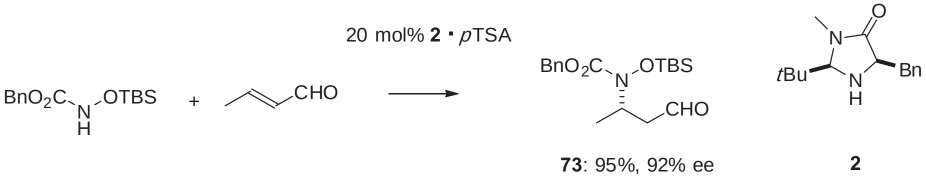
Conjugate addition of nitroalkanes to α,β-unsaturated aldehydes in the presence of imidazolyl-imidazolidin-4-ones was described by Arvidsson and coworkers [92].

In addition, silyl enol ethers of substituted acetophenones [93] or thioesters [94] react with α,β-unsaturated aldehydes under iminium-catalysis conditions in the sense of a Mukaiyama–Michael reaction (Scheme 4.24). Applications of this transformation can be found in the total syntheses of compactin [95] and homocitric acid lactone and its homolog [96].



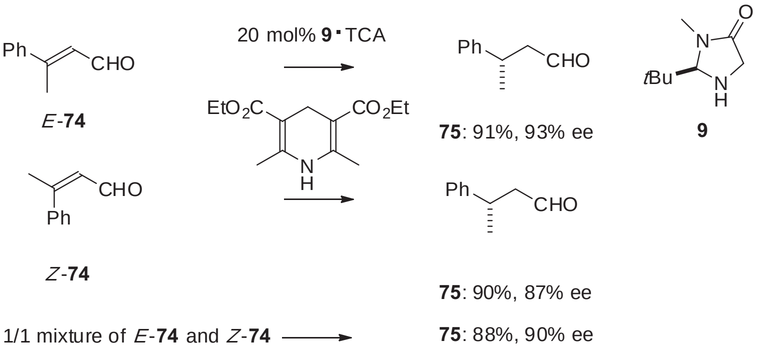
Scheme 4.24 Asymmetric Mukaiyama–Michael addition.

When used with *N*-silyloxycarbamates in the presence of catalytic amounts of chiral imidazolidin-4-ones, an aza-conjugate addition is observed. β-Amino-substituted aldehydes were isolated with high degrees of enantioselectivities (Scheme 4.25). Thus, by further chemical manipulations a short access to chiral β-amino acids is given [97].



Scheme 4.25 Asymmetric amine conjugate addition.

For asymmetric aza-Michael reaction of tetrazoles and triazoles see Reference [98]. In addition, asymmetric additions of hydride to conjugate systems were performed in the presence of catalytic amounts of imidazolidin-4-ones. Based on the role model of NAD as one of the coenzymes in oxireductases the Hantzsch ester was employed to deliver a hydride species in an asymmetric fashion when used with chiral imidazolidin-4-ones as catalysts. For a comprehensive overviews of results obtained in this field see Reference [99]. Successful examples were reported for both cyclic [100] and acyclic series [101]. Interestingly, both (*Z*)- and (*E*)-configured aldehydes **74** yield the same configured β-branched aldehyde **75** (Scheme 4.26). An (*E*)–(*Z*) isomerization prior to selective hydride delivery is assumed. When used with a 1 : 1 (*E*) : (*Z*) mixture of aldehyde **74,** the β-branched aldehyde **75** is isolated with 88% yield (90% ee). This methodology is of great significance for processes where starting materials of low geometric purity have to be used.

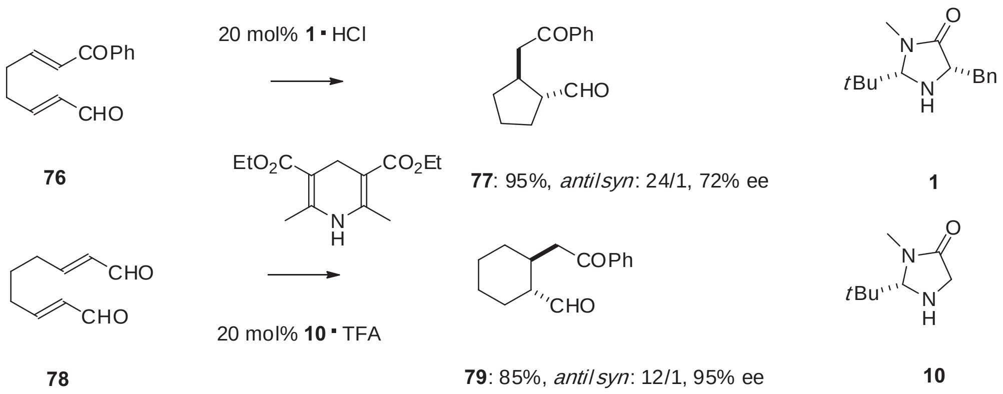


Scheme 4.26 Asymmetric transfer hydrogenation.

Asymmetric organocatalyzed hydride transfer was utilized in the total syntheses of spliceosome inhibitor 901464 [102], (+) neopeltolide [103], iriomoteolide-1b [104], (+)-neopeltolide [103], dysideaproline E [105], and ulapualide A [106]. For theoretical calculations on the origin of stereoselectivity of this process see Reference [107].

4.4
Cascade Reaction – Merging Iminium and Enamine Catalysis

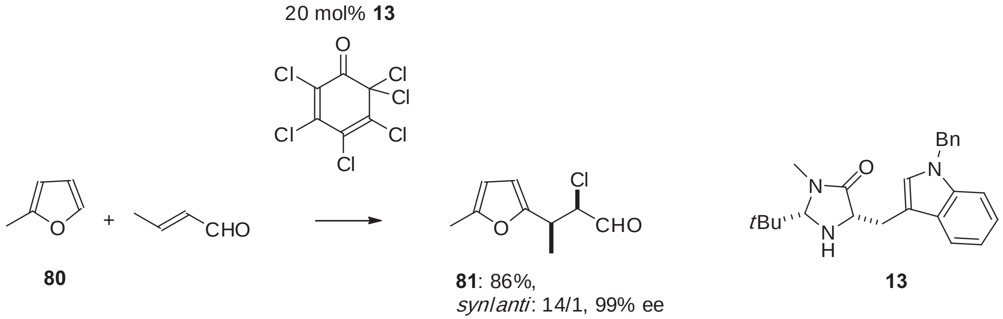
The utilization of both enamine- and iminium-activation enables rapid access to complex structures from simple starting materials. The first examples were reported for the deployment of one catalyst in these transformations. List and coworkers described a highly selective reductive Michael cyclization (Scheme 4.27). In a first catalytic cycle a hydride transfer occurs yielding an enamine inter-



Scheme 4.27 Reductive Michael cyclization.

mediate. A following intramolecular Michael addition yields keto-aldehydes **77** and **79** with high degrees of enantioselectivities. The high chemoselectivity in this transformation is particularly remarkable [108]. Subsequently, this cascade sequence was successfully utilized by the same group in the total synthesis of ricciocarpin A and several analogs [109].

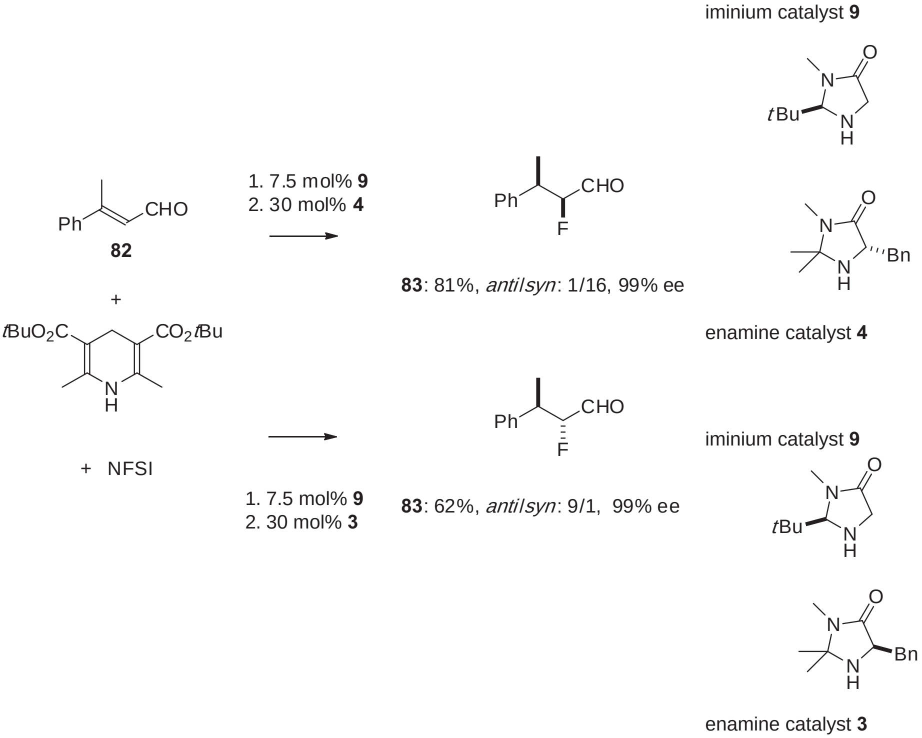
Furthermore, this concept was extended to cascade Michael-addition/α-chlorination. Thus, α-chloro-β-branched aldehydes **81** can be accessed with high degrees of stereoselectivities (Scheme 4.28) [110].



Scheme 4.28 Conjugate addition–chlorination cascade.

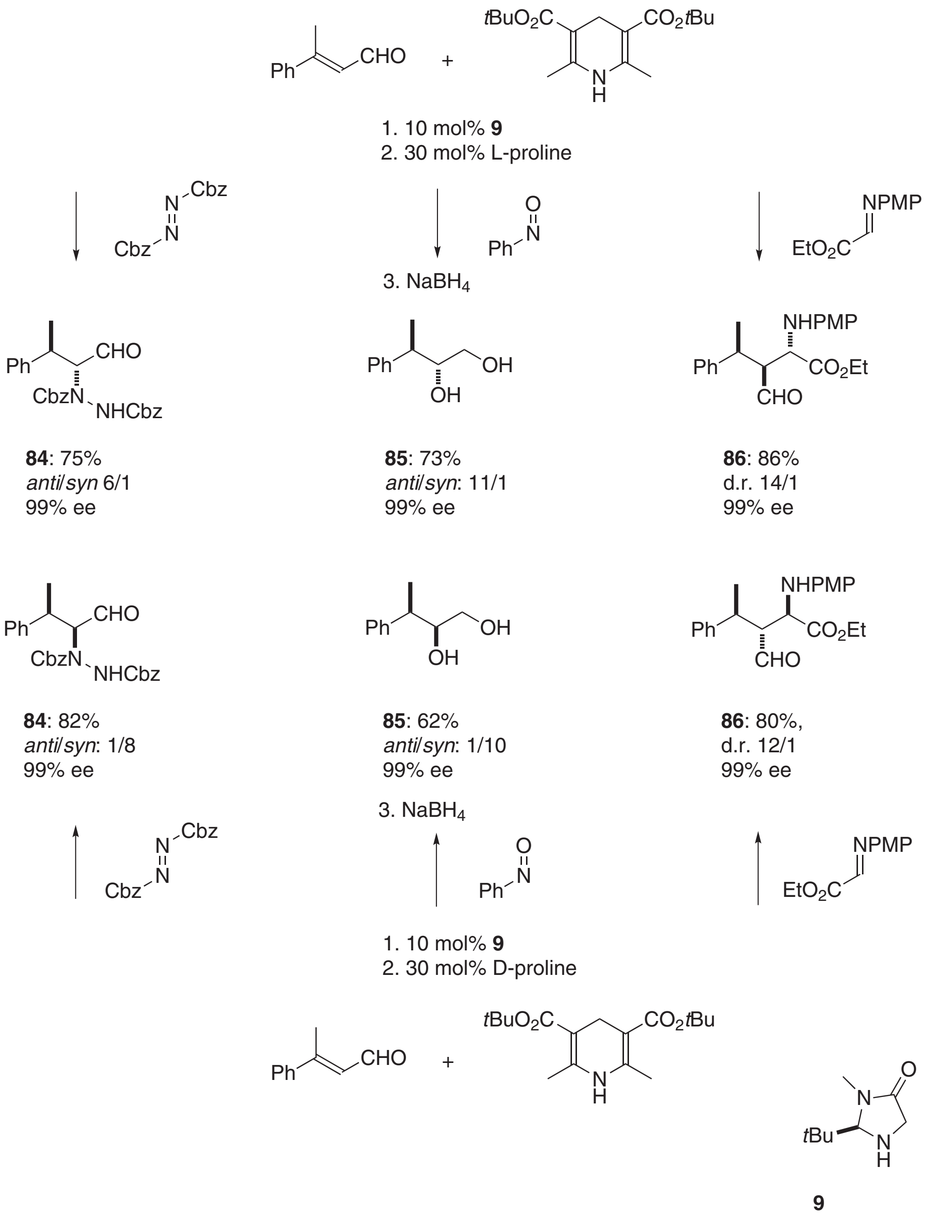
The discovery of two discrete amine catalysts that can increase selectivities in each step of this cascade reaction represents a further milestone of this development and has led to a more modulated stereoselective application of these cascade reactions. Practically enantiomerically pure *syn*- or *anti*-configured aldehydes can be accessed by a careful combination of two different imidazolidin-4-ones. The usefulness of this concept was demonstrated by the MacMillan group in several important transformations.

By application of iminium catalysis with the Hantzsch ester a series of reductive cascade reactions was realized. When used with NFSI (*N*-fluorobenzenesulfonimide) and Hantzsch ester an asymmetric reductive α-fluorination can be achieved. By suitable combination of two different configured imiadzolidin-4-ones, a defined and required installation of configuration is obtained. The first catalyst, the iminium catalyst, dictates the installation of configuration at the β-position, whereas the enamine catalyst determines the configuration at the α-position. Thus, when used with (*R*)-benzyl-imidazolidin-4-one **3** as the enamine catalyst instead of (*S*)-benzyl-imidazolidin-4-one **4** the corresponding *anti*-configured products **83** were detected with high degrees of enantioselectivities (Scheme 4.29) [110].



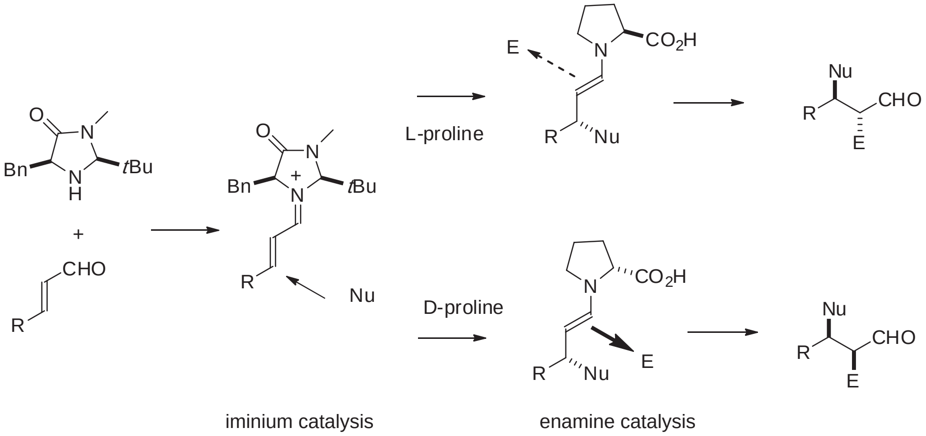
Scheme 4.29 Reductive fluorination with choice of configuration.

These findings were extended to a set of very useful cascade reactions by the MacMillan group [111]. In a first series 1,4-hydride additions were combined with aminations, oxidations, or Mannich reactions (Scheme 4.30). The hydride transfer was catalyzed by imidazolidinone **9**, whereas subsequent functionalization was realized by enamine catalysis through the deployment of proline. Depending on the chirality of proline used, optically pure *anti*- or *syn*-configured products **84–86** were isolated.



Scheme 4.30 Asymmetric cascade reactions.

Based on these results the following reaction pathway can be assumed. Iminium catalysis is realized by the use of chiral imidazolidinones. The subsequent enamine catalysis (HOMO activation) is realized by deployment of proline. The *anti*-configured products were detected by application of L-proline, whereas the use of D-proline determines the *syn*-configuration in the products (Scheme 4.31).



Scheme 4.31 Control of absolute and simple configuration in cascade reactions.

In a second series the same authors realized cascade reactions of conjugate addition/amination reactions. The corresponding highly substituted aldehydes **88** and **89** were isolated with enantioselectivities of 99% (Scheme 4.32).

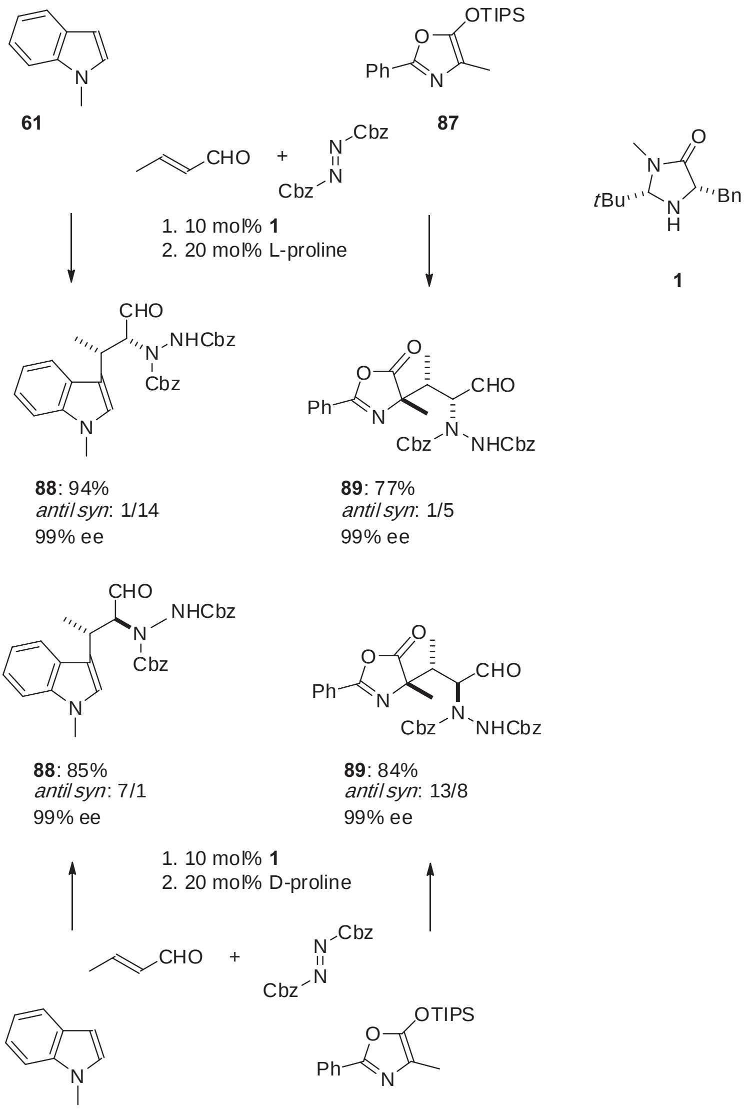
To demonstrate the power of this concept the sesquiterpene (–)-aromadendranediol was synthesized by the same authors using this cascade enamine–iminium activation concept.

For a merged metal catalyzed (cross-metathesis) and organocatalyzed (iminium/enamine) cascade reaction see Reference [111].

Different polymer-supported imidazolidin-4-ones have been deployed in cascade reactions. This strategy was successfully tested in a double Michael addition of methylindole, 2-hexenal, and vinyl methyl ketone [112].

To demonstrate the power of these cascade sequences this methodology was successfully applied to total syntheses of several indole-derived alkaloids, for example, minfiensine [113]. By implementation of organocatalyzed cascade reactions the MacMillan group was able to dramatically reduce the number of reaction steps in total syntheses of strychnine, aspidospermidine, and kopsinine [114].

The development and successful application of imidazolidones as organocatalysts has solved a great number of problems of synthetic organic chemistry. Moreover, this development creates extremely useful new asymmetric transformations, which were previously unknown to organic chemists. These reactions are characterized by operationally simple and very mild conditions, but nonetheless give high stereoselectivities and high yields. In particular, cascade reactions are of great interest because it is expected that by new modes of substrate activation new asymmetric synthetic transformations can be accomplished.



Scheme 4.32 Carba-Michael/amination cascade reaction.

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5
Oligopeptides as Modular Organocatalytic Scaffolds

Roberto Fanelli and Umberto Piarulli

5.1
Introduction

Peptides, either natural or synthetic, have found wide application in the field of biology, medicinal chemistry, and biotechnology as active compounds able to interact with several physiological and biochemical functions, and more recently as additives in food, cosmetics, and nutraceuticals [1]. This different behavior is due to the great structural diversity that can be achieved in even relatively short peptides, combining a small set of amino acids bearing different functional groups. In addition, the rigid backbone of amide bonds and the disposition of the side chains impart well-defined three-dimensional conformations typical of protein secondary structure elements: helices, turns, and sheets (Figure 5.1) [2].

Finally, peptides are chiral structures, and this is of fundamental importance in their interaction with biological receptors.

Notwithstanding these properties and the prominent role of enzymes as natural chiral catalysts capable of asymmetric transformations with outstanding selectivity (and also for industrial applications), peptides have only scarcely been used as catalysts in asymmetric applications, and only recently, after the blossoming of small organic molecules as enantioselective catalysts, has the value of peptide catalysts started to increase [3]. In particular, the first examples of peptide catalysts are related to the work of Inoue and Oku, who developed the application of a histidine-derived diketopiperazine (i.e., a cyclic dipeptide) to the enantioselective hydrocyanation of aldehydes, and Juliá and Colonna, who used poly-L-alanine peptides (with different lengths in terms of amino acid residues) in the enantioselective epoxidation of α,β-unsaturated ketones (see below). Curiously, somehow these two catalysts lie at two ends of a spectrum of possible peptide catalysts: a small rigid cyclic dipeptide in the case of the diketopiperazine and a large peptide that by virtue of its length is likely to adopt an ordered three-dimensional structure. In between these applications, more recently, several small linear peptides, composed of 2–10 amino acid residues, have been investigated as chiral organocatalysts. Thanks to their straightforward synthesis and their modular nature, as well as their ability to adopt a well-defined three-dimensional secondary structure suitable for the

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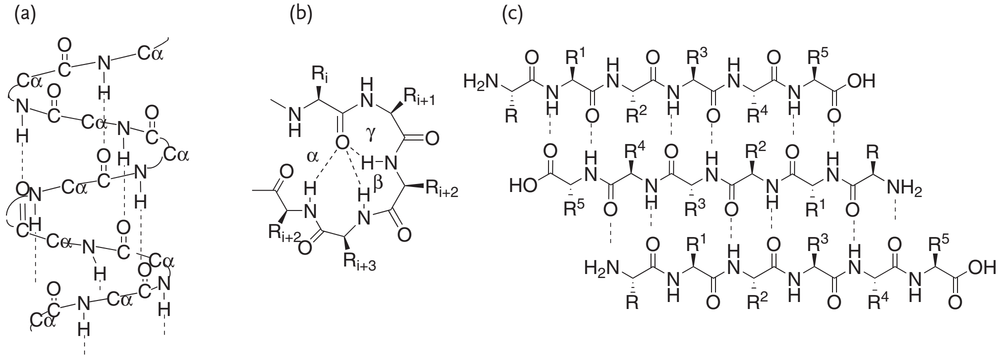


Figure 5.1 Schematic representation of peptide secondary structures: (a) helices (b) turns, and (c) sheets.

transfer of stereochemical information, several catalysts were recently prepared and tested. This chapter discusses the most relevant applications in terms of C–C bond forming reactions, as well as derivatization of alcohols and oxidations, with particular emphasis on rationalization in terms of reactive conformation of the catalytic peptide and activation of substrates as well as reagents by hydrogen bonds. These characteristics are probably the most relevant rationale behind the use of peptides as catalysts for asymmetric applications.

5.2
C–C Bond Forming Reactions

The development of asymmetric C–C bond forming reactions is an ongoing challenge in organic synthesis because they represent a very useful means of obtaining target products with high enantiomeric purity using catalytic amounts of a chiral compound. Proline and other simple organocatalysts have shown outstanding selectivity in several C–C bond forming reactions such as aldol, 1,4-conjugate addition, and Morita–Baylis–Hillman to name a few. Oligopeptides, however, possess greater reactivity than simpler organocatalysts, which allows the use of reduced catalyst loadings and reaction times.

The following subsections discuss the use of oligopeptides in aldol, Michael, Morita–Baylis–Hillman, and the hydrocyanation of aldehydes.

5.2.1
Aldol Reactions

The aldol reaction is one of the most efficient carbon–carbon bond forming reactions in organic chemistry. It combines an enol or an enolate with a carbonyl compound to yield a β-hydroxycarbonyl compound. Aldol reactions of simple

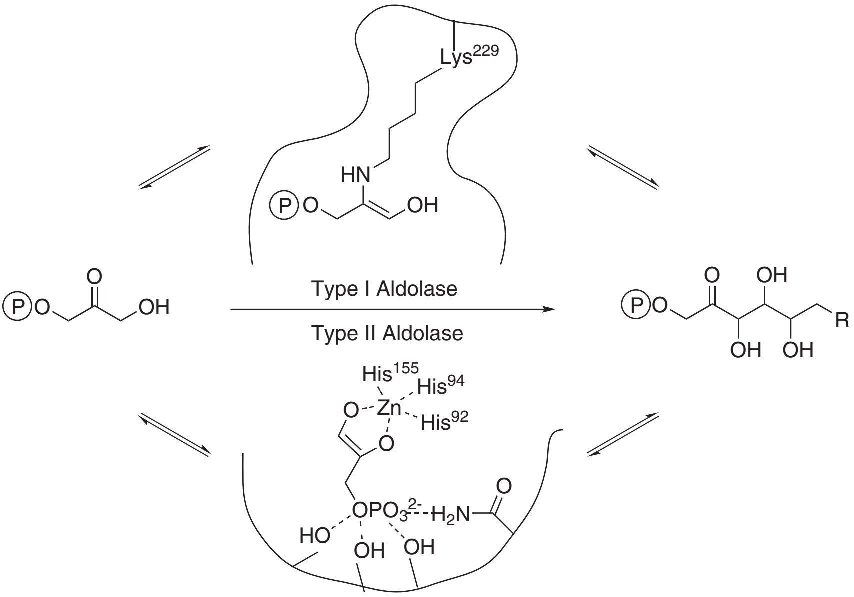


Figure 5.2 Aldolase mechanism pathways.

aldehydes, such as glycolaldehyde and formaldehyde, catalyzed by chiral amino acids present in carbonaceous meteorites have been invoked to explain the origin of prebiotic compounds, such as sugar [4].

In nature, aldol reaction is catalyzed by two different classes of aldolases: type I aldolases catalyze the reaction via enamine formation while with type II aldolases the reaction involves a zinc(II) ion [5] (Figure 5.2).

A wide range of small organic molecules, mainly secondary amines such as proline derivatives, promote asymmetric aldol reactions through enamine catalysis [6]. List, Reymond, Gong, and others reported the first examples of peptidic catalysts for aldol reactions [7]. In their report, Reymond and coworkers [7a] developed two classes of peptides, following two different designs. In the first peptide class a primary amine is present as a side chain residue (similar to the natural type I aldolase) or as free N-terminus; in the second a secondary amine or a proline residue is present at the N-terminus of the peptide, which incorporated at least one free carboxylic function (Figure 5.3).

Peptides containing either a primary amine (class I) or an acyclic secondary amine (class IIa) did not catalyze the reaction. Only terminal proline-containing peptides bearing a carboxylic acid group showed activity, although with moderate selectivity. Similar results were obtained by List [7b], confirming that the simultaneous presence of a carboxyl group and the prolyl derivative were necessary to achieve good conversions in peptide catalyzed aldol reactions [8].

Gong reported on the use of L-proline-based oligopeptides (from di- to hexapeptides were tested) that catalyzed the asymmetric direct aldol reaction of

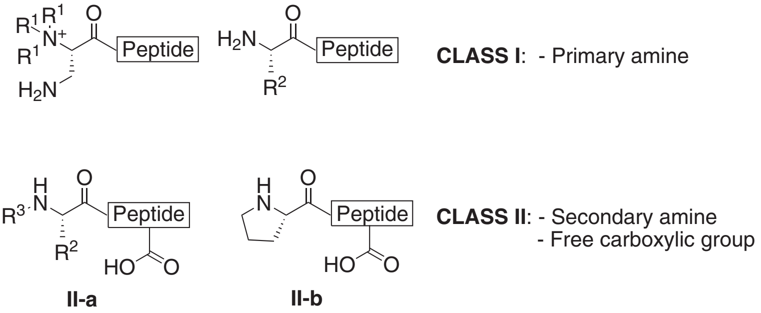
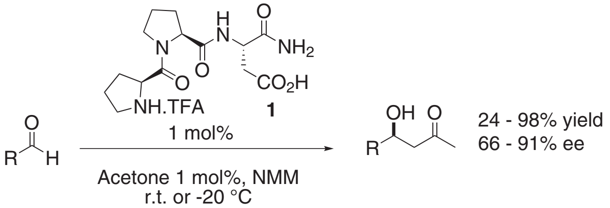


Figure 5.3 Design of potential peptide catalysts.

hydroxyacetone with aldehydes in aqueous media [7c]. Quite surprisingly, whereas the proline-catalyzed reaction yields the 1,2-diol product (i.e., the enolization occurs at the hydroxymethyl substituent of hydroxyacetone), in this case the aldol reaction preferentially occurred at the methyl group of hydroxyacetone to give mostly the 1,4-diol in good yields and enantioselectivities (ee of up to 87% using the pentapeptide Pro-Phe-Phe-Phe-Phe-OMe).

An important study was conducted by Wennemers and coworkers on the peptide catalyzed aldol reaction. In their studies a highly enantioselective tripeptide catalyst was identified among the members of a combinatorial library of 3375 tripeptides generated on a solid support by the split-mix methodology and screened without cleavage from the resin, by a "catalyst–substrate co-immobilization" technique [9]. The peptide catalysts and the ketone substrate were covalently linked to the solid support and reacted with a dyed aldehyde present in solution; active peptides catalyzed the reaction and the dyed product remained bound to the resin. Subsequent solution-phase experiments revealed that in particular the tripeptide Pro-Pro-Asp-NH_2 (**1**) is a highly active and selective catalyst: only 1% of peptide is sufficient to obtain the aldol product in 98% yield and 80% ee within 4 h at room temperature (Scheme 5.1) [10]. In comparison, 30 mol% of proline is required to obtain the products in comparable yields and enantioselectivities: that is, the higher complexity of the tripeptidic catalyst is an excellent trade-off for higher activity [8].



Scheme 5.1

Investigations of the secondary structure of the catalytic tripeptide Pro-Pro-Asp-NH_2 revealed that it adopts a turn-conformation in which the secondary amine and carboxylic acid are in close proximity and are both crucial for effective catalysis. It was also demonstrated that minor changes in the spatial arrangement of the secondary amine and the carboxylic function in the structure of these peptides can have significant effects on the catalytic properties [11]. Wennemers demonstrated also that the stereoselectivity of this peptide catalyst can be reversed using different solvents as reaction media. This is most likely due to a conformational switch from one turn conformation to another with the opposite twist, as indicated by circular dichroism investigations [12]. Finally, several different polymer-supported versions of H-Pro-Pro-Asp-NH_2 catalyst, as well as the effect of its loading on the resin, were investigated. Comparison of several resins (polystyrene, SPAR, TentaGel™, and PEGA) revealed TentaGel and PEGA as the optimal solid supports for maintaining the reactivity and selectivity with a catalyst loading as low as 0.1–0.2 mmol g^{-1}. A further extension was then shown PEGylating the catalyst to provide solubility in a broad range of common solvents (CH_2Cl_2, $CHCl_3$, THF, dioxane, acetone, DMSO, and H_2O).

Reiser and coworkers [13] developed a series of peptides containing the conformationally restricted *cis*-β-aminocyclopropylcarboxylic acid units (β-ACC) in combination with (L)-proline as catalysts for intra- and intermolecular aldol reaction. β-ACCs have been proven to greatly stabilize secondary structures even in short peptides when combined with natural α-amino acids. The short α,β-peptide H-Pro-β-ACC-Pro-OH (**2**) emerged as an effective catalyst of inter- and intramolecular aldol reaction either in organic or in homogeneous aqueous solvents, with complete conversions and excellent enantioselectivities (ee up to 99%). A conformational study suggested the existence of a privileged turn-like structure in which the C- and N-termini are close to each other (Figure 5.4).

5.2.2
Michael Reactions

The Michael reaction is the 1,4-conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl or β-electron-poor vinyl compounds and, as such, represents a useful method for the mild formation of C–C bonds. Similarly to aldol reactions,

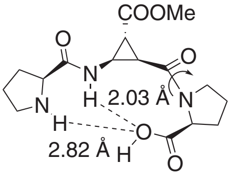


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Figure 5.4 Low-energy turn like structure of peptide H-Pro-β-ACC-Pro-OH.

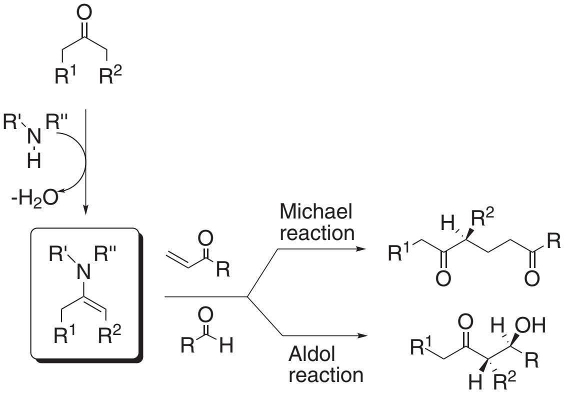
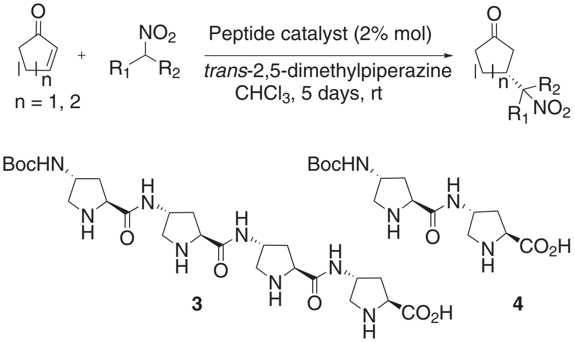


Figure 5.5 Michael reaction versus aldol reaction.

Michael reactions catalyzed by prolyl peptides proceed via the initial formation of an enamine, which subsequently reacts with its electrophilic partner (Figure 5.5).

Short peptides have been used both to catalyze the conjugate addition of nitroalkanes to α,β-unsaturated ketones, and the addition of enolates of aldehydes to nitroolefins.

Tsogoeva and coworkers reported the use of oligopeptides of 4-*trans*-aminoproline (tetra- and dipeptides **3** and **4**, respectively) as organic catalysts for the Michael reaction of nitroalkanes to cyclic enones. The reaction, in the presence of the achiral additive *trans*-2,5-dimethylpiperazine, afforded the conjugate addition product in excellent yield and ee up to 88% (Scheme 5.2) [14]. Other dipeptides, with a primary amine at the N-terminus and containing a histidine derivative, were definitely less selective [15] (under the same reaction conditions), while L-proline alone afforded the same product in 93% ee [16].



Scheme 5.2

Conversely, the reverse approach, that is, the addition of aldehyde and ketone enolates to nitroolefins, gave better results using short peptides than proline.

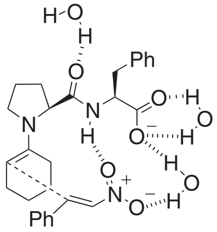
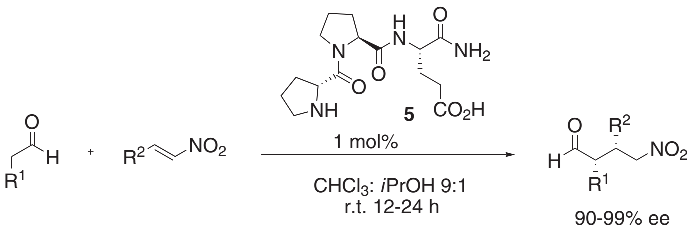


Figure 5.6 Proposed transition state for the nitro-Michael reaction catalyzed by H-Pro-Phe-OH.

Tsogoeva and coworkers tested prolyl-peptides in the nitro-Michael reaction using water as solvent without the addition of any organic co-solvents. The prolyl peptides, and in particular H-Pro-Phe-OH, as their sodium salts generated *in situ* by addition of equimolar amounts of NaOH, catalyzed the addition of ketones, and in particular cyclohexenone, to aromatic nitroolefins in very good yield and moderate enantioselectivity [17]. In a transition state proposed by Tsogoeva, water plays a triple role; in fact it is involved in hydrogen bonds with the proline amide oxygen atom and with the carboxy terminal group of the phenylalanine, and it also forms a hydrogen bond interaction with the nitro-group of the olefin (Figure 5.6).

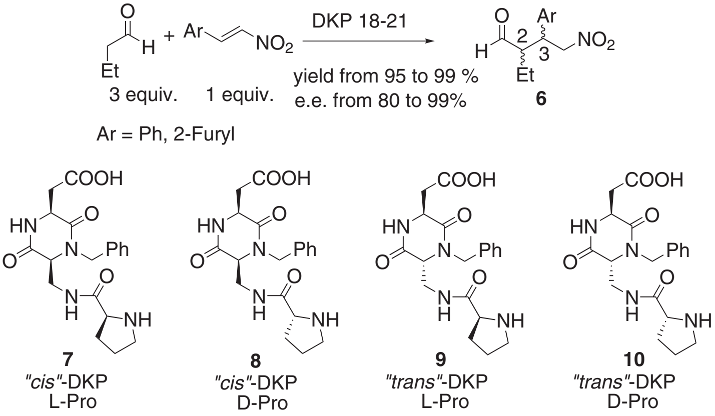
Wennemers and coworkers reported that the tripeptide Pro-Pro-Asp-NH_2 (**1**), which was developed as a powerful catalyst in the organocatalyzed aldol reaction, was also found to be a very enantioselective catalyst in the conjugate addition of aldehydes to nitroolefins [18]. A structure optimization was then undertaken, revealing that better results could be achieved using the tripeptide D-Pro-Pro-AspNH_2 (**5**) and D-Pro-Pro-GluNH_2. The activity and selectivity of these catalysts was attributed to their bifunctional nature, with the secondary amine promoting the formation of the enamine and the carboxylic group activating the nitroolefin moiety through Brønsted acid catalysis. In this way, no additives are necessary for the high catalytic efficiency these catalysts, unlike for many other amine based catalysts, which require the addition of catalytic/sub-stoichiometric acids and/or bases. The spatial disposition of these catalytically active groups is also extremely important; an X-ray crystal structure determination revealed that the tripeptide D-Pro-Pro-AspNH_2 adopts in the solid state a β-turn structure. A range of aldehydes (linear or β-branched aliphatic aldehydes) and nitroolefins (including aromatic nitroolefins bearing both electron-poor and electron-rich aromatic substituents, as well as aliphatic nitroolefins) reacted readily, in the presence of 1 mol% of the catalyst. The resulting γ-nitroaldehydes were obtained in excellent yields and stereoselectivities within 12–24 h at room temperature (Scheme 5.3).

Piarulli and coworkers recently reported the preparation of peptidomimetic organocatalysts starting from two bifunctional diketopiperazines (DKPs) formally derived from the head-to-tail cyclization of L-aspartic acid and either (*R*)- or (*S*)-2,3-diaminopropionic acid and, therefore, featuring an aminomethyl and a



Scheme 5.3 Conjugate addition of aldehydes to nitroolefins.

carboxymethyl side arms at positions 3 and 6 of the 2,5-piperazinedione ring. The terminal amino group of the DKP scaffold was coupled to a L- or D-proline residue, giving rise to the four different organocatalysts **7–10.** These were tested in the conjugate addition reaction of several aldehydes to β-nitrostyrene and (*E*)-2-(furan-2-yl)nitroethene with excellent diastereo- (99 : 1 dr) and enantioselectivities (up to 98% ee) in high yields under operationally mild conditions (Scheme 5.4). The absolute configuration of the conjugate addition products depended on the configuration of the terminal proline residue [19].



Scheme 5.4

To rationalize these results, a conformational study of these peptidomimetics was undertaken. DKP scaffolds can induce a well-defined tridimensional structure and the importance of this characteristic was proven in several studies [20]. In fact, as a consequence of the absolute configuration of the two α-amino acids forming the cyclic dipeptide unit, the two reactive functionalities (amino and carboxylic acid) are locked in a cis- (catalysts **7** and **8**) or trans-configuration (catalysts **9** and **10**).

A Monte Carlo/energy minimization (MC/EM) conformational search for the enamine intermediate derivatives revealed conformations where one face of the

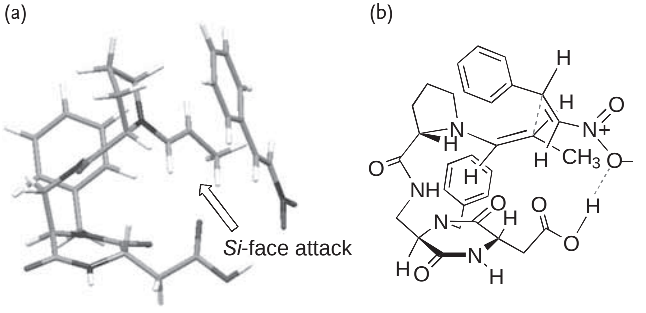


Figure 5.7 (a) Enamine intermediate of catalyst **9** with propanal: low energy conformation featuring *Si* face attack; (b) proposed transition-structure model for the reaction of the propanal enamine of **9** with β-nitrostyrene, leading to (2*R*,3*S*)-2-methyl-4-nitro-3-phenylbutanal.

enamine moiety is shielded by the diketopiperazine ring and the carboxylic acid is likely to act as a hydrogen-bond donor, activating the nitroolefin acceptor (-NO_2) and directing its approach from the less hindered enamine face (Figure 5.7).

5.2.3
Morita–Baylis–Hillman Reactions

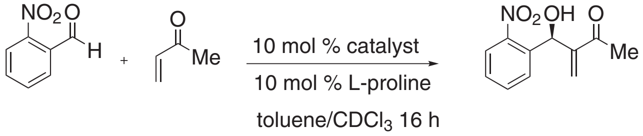
The Morita–Baylis–Hillman (MBH) reaction is described as the coupling between the α-position of an activated double bond and an sp^2 electrophilic carbon (typically an aldehyde, but also an imine) using an appropriate catalyst, normally Lewis bases [21]. Shi and coworkers showed that imidazole and proline formed an efficient co-catalytic system for carrying out the MBH reaction, but with low ee [22].

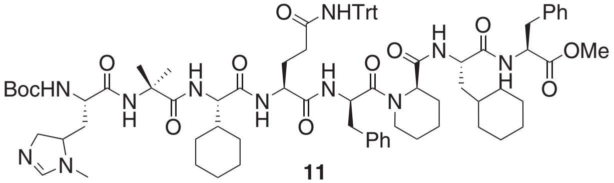
Based on these observations, the group of Miller set out to screen peptide catalysts, containing N-terminal π-methyl histidine (Pmh), in the MBH reaction of methyl vinyl ketone (MVK) and *p*-nitrobenzaldehyde with a co-catalytic quantity of L-proline [23]. Several oligopeptide libraries, generally biased towards β-hairpin scaffolds, were screened, showing that the presence of Pmh followed by a residue of 2-aminoisobutyric acid (Aib) was essential to achieve an enantiomeric excess. Higher selectivities were also observed increasing the chain length, with heptameric and octameric sequences apparently increasing the enantioselectivity of the reaction, which, however, reached a plateau with a further increase in the number of residues. The best results were obtained with octapeptide **11**, which afforded the desired condensation product of 2-nitrobenzaldehyde with MVK in 78% ee and high (>75%) conversion (Table 5.1).

An optimization of the co-catalyst was also attempted, using other amino acids as well as several proline derivatives, but with no positive results.

To rationalize the cooperative intervention of the co-catalytic system (Pmh-containing peptide and proline), two possible transition states were proposed. The first contains a proline-enamine intermediate (Figure 5.8a) with the histidine

Table 5.1 Catalyst screen for the MBH reaction of methyl vinyl ketone with 2-nitrobenzaldehyde.



Entry	Catalyst	ee (%)
1	Boc-Pmh-OMe	19
2	Boc-Pmh-Aib-OMe	33
3	Boc-Pmh-Aib-Phe-OMe	33
4	Boc-Pmh-Aib-Phe-D-Phe-OMe	40
5	Boc-Pmh-Aib-Cha-hPhe-D-Phe-OMe	47
6	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-Phe-OMe	61
7	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-(Boc)Trp-Phe-OMe	73
8	 **11**	78
9	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-D-Pip-Cha-Phe-Phe-OMe	75
10	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-D-Pip-Cha-Val-(Boc)Trp-Phe-OMe	74

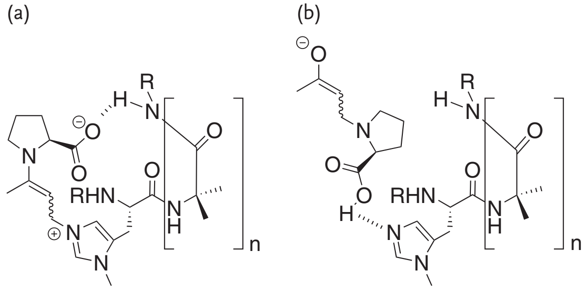
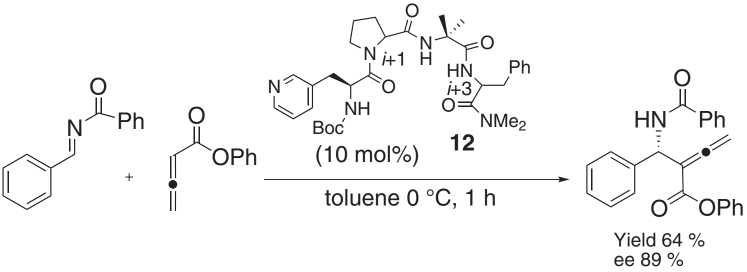


Figure 5.8 Possible transition state assemblies involving (a) proline-enamine intermediates and (b) peptide–proline–MVK conjugate addition product intermediates.

nitrogen acting as the nucleophilic catalyst, while in the second hypothesis a peptide–proline–MVK adduct issued from the conjugate addition of proline (Figure 5.8b) is temporarily formed.

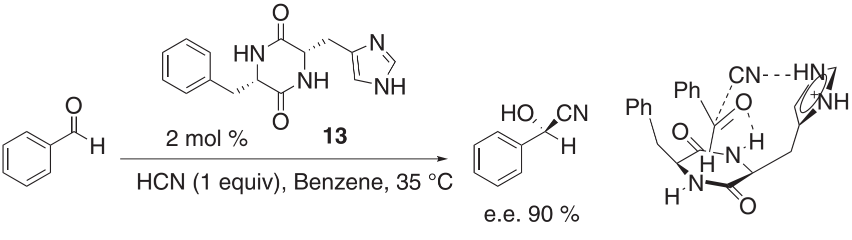
A closely related transformation was reported by the group of Miller, who used 3-pyridylalanine (Pal) based catalysts for the enantioselective addition of allenoates to *N*-acyl imines (Scheme 5.5) [24]. Tetrapeptide **12**, biased to adopt a β-turn, with a D-Pro-Aib sequence between Boc-Pal and the terminal amino acid, proved particularly effective both in terms of reactivity and selectivity, yielding the α-allenylidene-β-aminoester derivatives in good yield and ee. Interestingly, there was no reaction with Pmh-containing catalysts, while Boc-Pal-OMe alone gave the reaction product in good yield, but as a racemic mixture. Here, the gain in using peptides with a well-defined secondary structure is evident in the enhanced stereoselectivity of the reaction.



Scheme 5.5

5.2.4
Hydrocyanation of Aldehydes

A groundbreaking study in the field of organocatalysis with peptides was published in 1979 by Oku and Inoue, showing that cyclic dipeptides are valuable catalysts for the asymmetric addition of hydrogen cyanide to benzaldehyde to give the corresponding cyanohydrins (Scheme 5.6) [25]. Synthetic diketopiperazine **13** (cyclo-L-phenylalanine-L-histidine), in which the imidazole group of the histidine residue is catalytically active as a base, afforded (*R*)-mandelonitrile in 90% ee in only 30 min [26].



Scheme 5.6

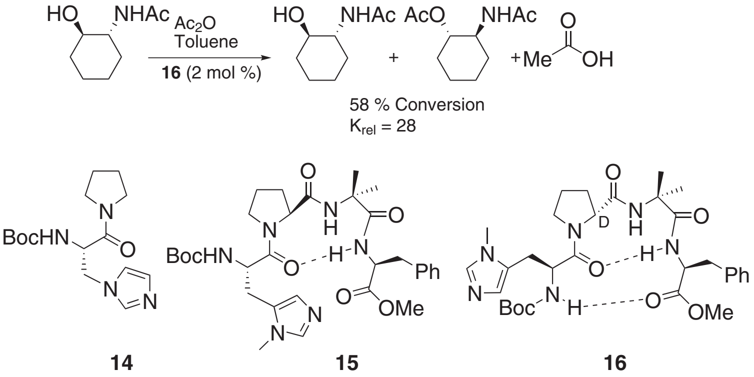
A rationale for the stereoinduction was provided, whereby the role of histidine is to direct the attack of cyanide to the *Si*-face of benzaldehyde while the *Re*-face is blocked by the aromatic ring of the phenylalanine residue. Further work reported how time, temperature, solvent, and crystallization of the catalyst all play a significant role in an enantioselective reaction [27].

5.3
Asymmetric Acylations

An important application of peptide organocatalysts is their use in the kinetic resolution of alcohols. This selectivity is due to the ability to activate only one enantiomer of the substrate while the other remains inert.

Miller and coworkers have shown that short peptides containing *N*-alkylated histidine residues can be used as catalyst for the enantioselective acylation of secondary and some tertiary alcohols. The *N*-alkylated histidine residues are postulated to facilitate acylation by a nucleophilic mechanism, whereas the backbone amides and side chain functionalities are supposed to govern the selectivity through enantiomer-specific secondary contacts (hydrogen bonding, π-stacking, ion pairing, etc.) [28].

The β-turn conformation of these peptides was imparted by the sequence Pro-Aib, a well-known β-turn inducer (Scheme 5.7) [29].



Scheme 5.7

Catalyst **14**, which lacks any secondary structure, is in fact ineffective as asymmetric catalyst, thus confirming the relevance of a well-defined spatial conformation.

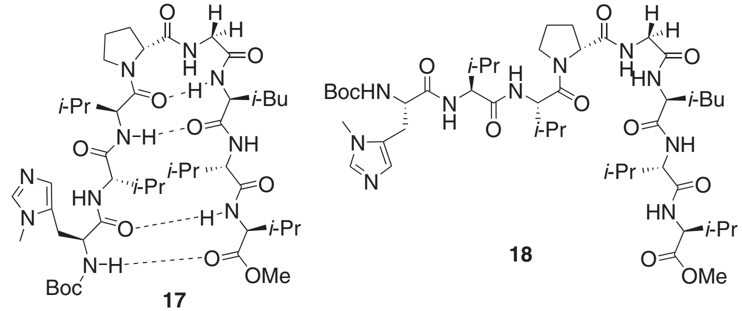
Peptides **15** and **16** differ in the stereochemistry of the proline residue. It was demonstrated that the stereogenic center governs the sense of enantioselectivity, leading to the formation of opposite enantiomers of a given substrate. Furthermore peptide **16**, containing D-Pro, adopts a more rigid β-hairpin conformation, presenting two intramolecular hydrogen bonds. This conformational rigidity may also explain the difference in terms of enantioselectivity [30].

This was confirmed in a subsequent work of Miller and coworker where a series of octapeptides containing N-terminal π-methyl histidine (Pmh) was developed (Figure 5.9) [31].

Peptide **17**, which presents a more stable secondary structure, gave better results in terms of enantioselectivity.

The stereoselectivity was improved through the preparation of pentapeptide **19**, in which the oxygen of the amide between proline and the Aib residue was replaced by a sulfur atom, with the thioamide considered as an isostere of the amide. The NH of a thioamide can form a stronger hydrogen bond than an amide NH considering its more acidic character [32]. A further improvement was reported with the insertion of a sulfonamide; in fact the tosyl group on the α-amino of the histidine residue enhances the stability of the second interstrand hydrogen bond in the β-hairpin structure [33].

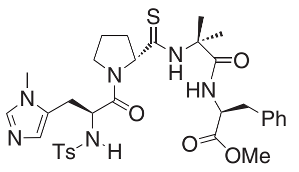
The enhanced stereoselectivity obtained with peptide **19** confirms that conformational rigidity and, therefore, a more stable β-hairpin conformation is an important requirement for a good chiral stereoselective catalyst (Figure 5.10).



17

18

Figure 5.9 Octapeptides containing N-terminal π-methyl histidine.

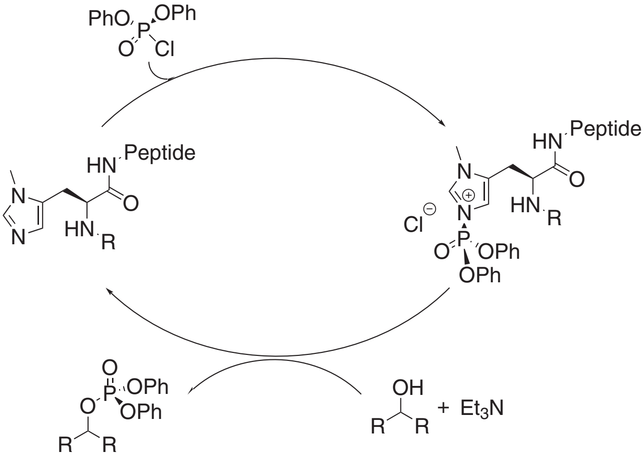


19

Figure 5.10 Thioamide stabilized β-hairpin peptide **19**.

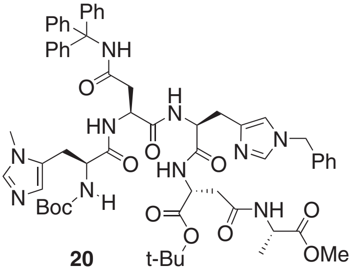
5.4
Asymmetric Phosphorylations

Phosphorylation is a process involved in many cellular pathways such as activation or deactivation of enzymes. An extensive study of enantioselective phosphorylation reactions was reported by Miller and coworkers using several π-(Me)-histidine containing peptides. The proposed catalytic cycle involves the generation of an high energy phospho-imidazolium ion and its reaction with the alcohol substrate in a site-specific manner. Following this mechanism, regio- and enantiopure phosphorylated alcohols can be prepared (Scheme 5.8).



Scheme 5.8 Catalytic cycle for peptide-catalyzed asymmetric phosphorylation.

A small library of 39 peptides was screened for the regioselective phosphorylation of compound **21** [34]. Each peptide afforded different extents of enantioselectivity, highlighting how the secondary structure can play an important role in influencing the stereochemical course of the reaction. Remarkably, peptide **20** afforded the desired product as a single enantiomer with >98% ee (Scheme 5.9).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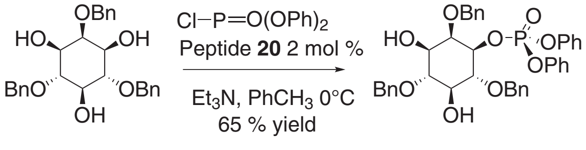


21 **22** > 98 % ee

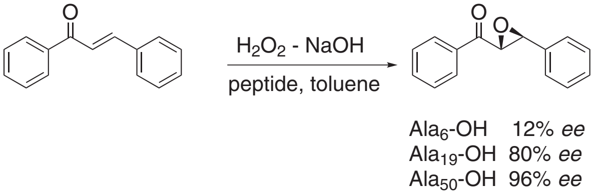
Scheme 5.9 Peptide-catalyzed desymmetrization of a *meso*-inositol derivative.

5.5
Enantioselective Oxidations

Juliá and Colonna in the 1980s described the asymmetric epoxidation of chalcones by using polypeptides such as poly-alanines and poly-leucines [35].

Such polypeptides assume α-helical structures in which the three or four terminal NH protons of amides are not involved in intramolecular hydrogen bonds and are relevant for asymmetric induction [36].

Depending on the number of alanine residues, the epoxide product from chalcone could be obtained in up to 96% ee (Scheme 5.10).



Scheme 5.10 Juliá–Colonna epoxidation.

The initial triphasic system (polyamino acid, aqueous phase, organic phase) used for this reaction presented the drawbacks of a long reaction time and, more importantly, difficult recovery of the catalyst. This problem was overcome by immobilizing the catalyst on a solid support [37].

Berkessel *et al.* addressed the question of identifying the "minimal catalophore" (i.e., the minimum peptide length for catalytic activity). For this purpose, they synthesized a library of L-Leu oligomers (1–20 mer) on TentaGel, and tested these solid-phase-bound oligopeptides in the Juliá–Colonna epoxidation [38]. This work revealed that as few as five L-Leu residues are sufficient for the epoxidation of chalcone to take place with 96–98% enantiomeric excess. The result strongly suggests that one turn of a helical peptide is the minimal structural element required for catalysis.

Chiral oligopeptides containing α,α-disubstituted cyclic amino acids to induce an α-helical structure were developed by Tanaka [39]. For these peptides an increase in enantioselectivity was also observed in relation with peptide length. Using 5 mol% of the N-terminal free nonamer containing the cyclic amino acid **26**, highly enantioselective epoxidation of α,β-unsaturated ketones was completed. The N-terminal free peptide gave better enantiomeric excesses than the Boc-protected peptides (Figure 5.11).

Miller and coworkers reported that well-defined peptide-based catalysts are able to induce asymmetric epoxidation of cyclic alkenes bearing amide or carbamate moieties close to the alkene (Scheme 5.11). The catalyst is based on transient generation of peptide-based peracids in a catalytic mode with turnover [40]. For the functional evaluation of catalyst **27**, different analogs were prepared. First, the

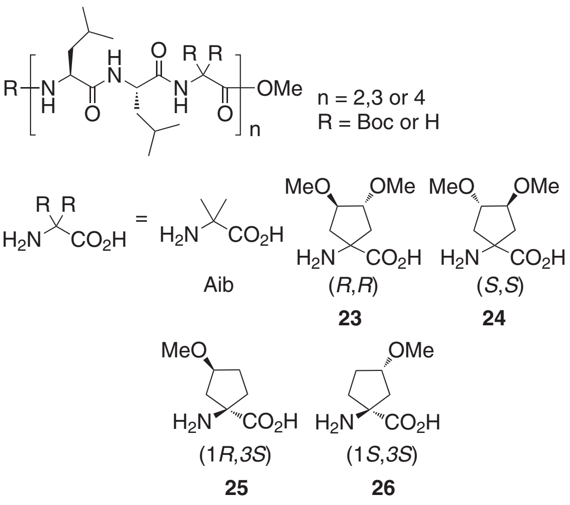
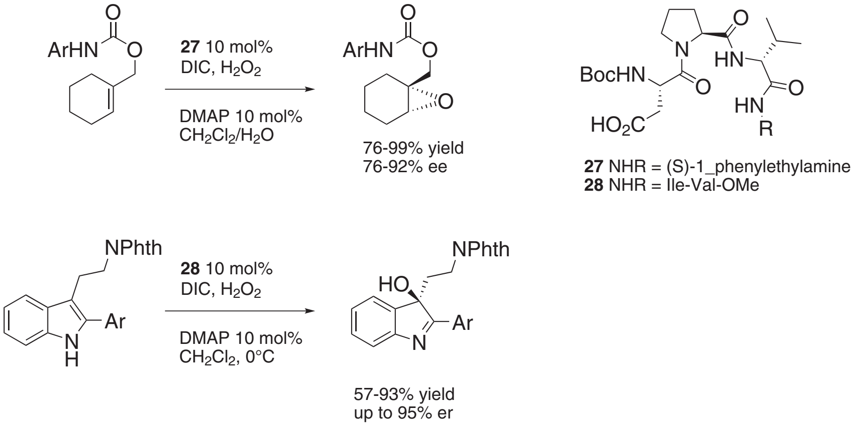


Figure 5.11 Structures of α,α-disubstituted amino acids and their peptides.

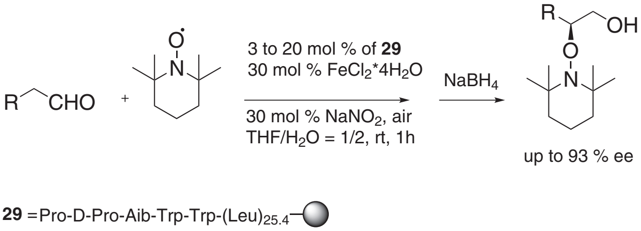


Scheme 5.11

NHBoc functionality was replaced with a methyl group. In a second case the pro-D-Val amide was replaced with an alkene isostere or with a fluoroalkene moiety. In all cases these modifications led to lower enantioselectivity [41].

More recently Miller and Movassaghi applied peptide catalyst **28** in the chemoselective oxidation of many indoles to the corresponding hydroxyl-indolenines, obtaining significant levels of enantioselectivity in this catalytic asymmetric indole oxidation [42].

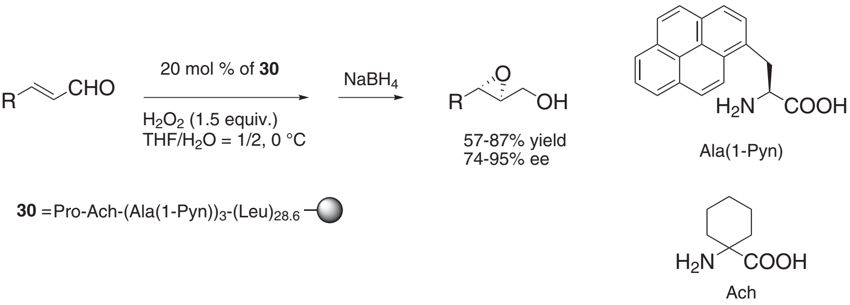
Kudo and coworkers developed a poly(ethylene glycol)–polystyrene (PEG-PS) resin supported peptide catalyst possessing poly-leucine as a chiral hydrophobic chain [43]. This catalyst has a β-turn pentapeptide connected to the N-terminus of the α-helical poly-leucine chain. This resin-supported peptide catalyst was effective for the asymmetric α-oxyamination of aldehydes, particularly in aqueous media (Scheme 5.12). It could also be shown that peptide derivatives lacking the poly-leucine fragment, or where the poly-leucine was substituted with poly-isoleucine or poly-valine, were less effective in terms of yield and enantioselectivity, proving that the structure and chirality of the hydrophobic segment are important for the reaction rate and enantioselectivity.



Scheme 5.12

More recently, the asymmetric α-oxyamination of aldehydes catalyzed by peptide **29** in combination with oxidative enzyme laccase was reported [44]. This combination promoted the reaction smoothly in water without employing a metal reagent and both the oxyaminated aldehydes and carboxylic acids could be obtained depending on the reaction conditions.

The enantio- and diastereoselective epoxidation of α,β-unsaturated aldehydes in aqueous media was also performed by using the poly-leucine resin supported peptide catalyst developed by Kudo [45]. It was that the novel terminal sequence D-Pro-Ach-[Ala(1-Pyn)]$_3$ possessing a highly hydrophobic and bulky aromatic ring was particularly effective (Scheme 5.13).



Scheme 5.13

5.6
Hydrolytic Reactions

Enzymatic hydrolysis has been widely studied and several examples of the asymmetric hydrolysis of esters catalyzed by single amino acids, polypeptides, and dendrimers catalyzed have been reported [46].

Uoeka and coworkers focused their efforts on the development of a catalytic system of a dipeptide or tripeptide containing L-histidine [47]. An enhanced enantioselective hydrolysis was obtained with a tripeptide catalyst in a mixed surfactant system. The tripeptide *Z*-L-Phe-L-His-L-Leu-OH was the most efficient catalyst for the hydrolytic cleavage of *p*-nitrophenyl *N*-acylphenylalanylates.

Conformational studies on the tripeptide *Z*-L-Phe-L-His-L-Leu-OH and the dipeptide *Z*-L-Phe-L-His-OH show that both compounds share the same specific circular dichroism patterns. The tripeptide shows an α-helix-like CD spectrum.

5.7
Summary and Conclusions

Over the last decade peptides have shown a great potential as organic catalysts, with unique characteristics of reactivity and chemo- and stereoselectivity that are difficult to achieve with different types of organic catalysts. Their reactivity can be achieved by the use of properly functionalized natural or unnatural amino acids, whereas their spatial properties, which are typical of the secondary structure of proteins (in particular α-helices and β-turns) and are defined by the sequence of amino acids, are able to tune the reactivity of the catalysts, often enhancing them so that lower catalyst loadings are necessary. An essential role in this process is played by the network of hydrogen bonds among the amino acid residues, as well as with the substrate and reagents, which is only possible in the presence of several well-defined and organized amino acid residues.

In addition, their ease of synthesis and modular nature allows for a simple tuning of the catalytic activity through the synthesis of combinatorial libraries of catalysts, thus allowing optimization of their structure with respect to the substrate and reaction under investigation.

In conclusion, oligopeptides are being established as a versatile alternative to enzymes and small synthetic catalysts in many different reactions and can be expected to prove valuable asymmetric catalysts for more and more synthetically useful transformations in the next decade.

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Part II
Non-Amino Acid-Derived Catalysts

6
Cinchonas and Cupreidines

Steen Ingemann and Henk Hiemstra

6.1
Introduction

Cinchona alkaloids are well-known natural products with a fascinating medicinal history and an intriguing molecular structure that is responsible for their use in chemistry [1, 2]. The natural cinchona alkaloids are obtained from the bark extract of the *Cinchona* tree and consist of quinine, quinidine, cinchonine, and cinchonidine with the structures shown in Figure 6.1.

The natural cinchona alkaloids feature a quinuclidine moiety, a quinoline part, a secondary alcohol, and a vinyl or ethyl group attached to C3 of the quinuclidine unit (Figure 6.1). They have five stereogenic centers (N1, C3, C4, C8, and C9), but differ in absolute configuration only at N1, C8, and C9. The configuration is the same at C3 and C4 in the quinuclidine part and the diastereoisomeric pairs (quinine, quinidine and cinchonine, cinchonidine) are commonly referred to as pseudo-enantiomers. The unique stereochemistry of natural cinchona alkaloids in combination with the ready accessibility is largely responsible for their widespread application in asymmetric organocatalysis [3]. In addition, they are used as ligands for transition metal complexes [4] and as components of chromatographic stationary phases and bases for the resolution of racemates [5].

Interest in the field of asymmetric catalysis with cinchona alkaloids has increased tremendously in the last decade as part of the sudden explosion of interest in organocatalysis. Preceding the present interest in cinchona alkaloids, these compounds were reported as chiral promoters in organic reactions as described in several reviews [3]. Briefly, the earliest examples of the use of cinchona alkaloids are the addition of HCN to benzaldehyde as reported by Bredig and Fiske 1912 [6], the work of Pracejus in 1960 on the addition of methanol to phenyl methyl ketene [7], and the pioneering work by Wynberg and coworkers, who showed that cinchona alkaloids can serve as catalysts for various enantioselective reactions [8], such as the conjugate addition of thiols to α,β-unsaturated ketones [9]. Until the late 1990s, the cinchona alkaloids and derivatives were mainly applied in phase-transfer catalysis, for example, in the asymmetric alkylation of glycine imino esters [10] and in asymmetric dihydroxylation and

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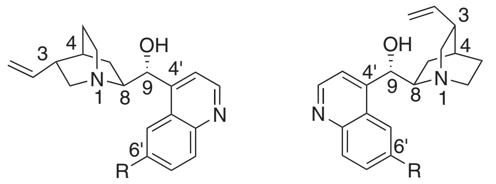
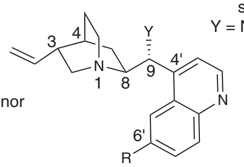


1 R = OMe quinine
2 R = H cinchonidine
3 R = OH cupreine

4 R = OMe quinidine
5 R = H cinchonine
6 R = OH cupreidine

Figure 6.1 Structures of the natural cinchona alkaloids and of cupreine and cupreidine. The analogs of quinine, quinidine, cinchonidine, and cinchonine with an ethyl at C3 (the dihydro species) are also isolated from natural sources.



Y = OH as hydrogen bond donor
Y = OR, OC(O)R, carbamates, OPR_2
Y = thioureas, quanidines squaramides, sulfonamides as hydrogen bond donors
Y = NH_2 in aminocatalysis

Quinuclidine *N*

- general base, deprotonation
- *N* prototonation leads to hydrogen bond donor
- nucleophilic catalyst
- *N*-alkylation, phase transfer catalysis

R = OH and thioureas as hydrogen bond donors

Figure 6.2 Sites in natural cinchona alkaloids for preparing derivatives for asymmetric catalysis.

aminohydroxylation [11]. Succeeding these early studies, numerous reports have appeared concerning organocatalysis with cinchona alkaloids and synthetically prepared derivatives thereof.

6.2
Cinchona Alkaloid Derivatives

In terms of structure, the natural cinchona alkaloids possess several sites that are highly suited for the introduction of new functionalities that enhance their use as catalysts for asymmetric synthesis (Figure 6.2). Examples are amine, ether, ester, urea, thiourea, squaramide, or guanidine functions at the C9 or at the C6′ position (Figure 6.3). In addition, other species have been applied, such as quaternary ammonium salts obtained by alkylation of the quinuclidine N atom and the ether-bridged dimers applied in the Sharpless asymmetric dihydroxylation (Figure 6.3) [11]. Less frequently used derivatives of the natural cinchona alkaloids include catalysts with the quinoline being replaced by a naphthalene moiety or with a large aromatic group at C6′.

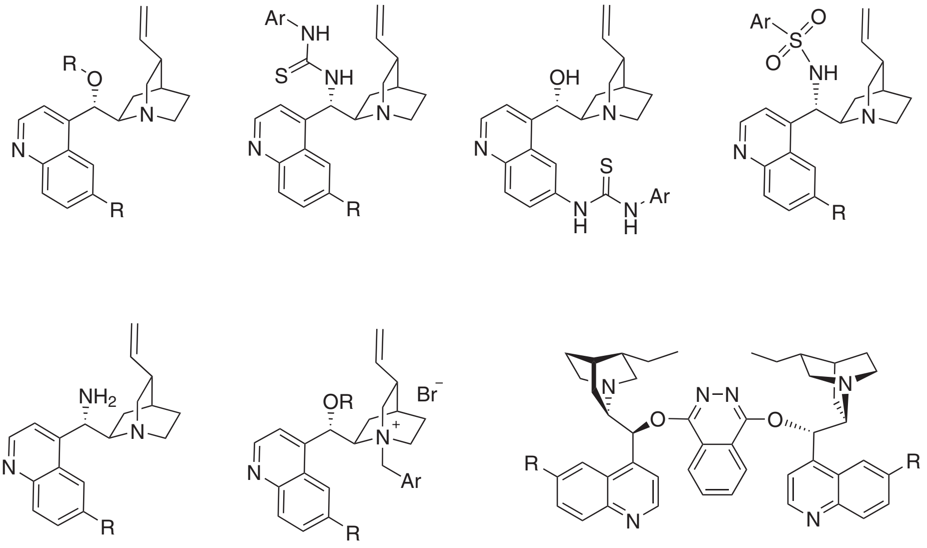


Figure 6.3 General structures of derivatives of cinchona alkaloids (R = H, OH, OMe).

6.3
Natural Cinchona Alkaloids, Cupreine, and Cupreidine

6.3.1
Structural Properties

The catalytic properties of the natural cinchona alkaloids are related to the presence of a basic tertiary amine function (of the quinuclidine ring) and the hydrogen bonding properties of the hydroxyl group of the C9 site. In addition, the conformational behavior of these molecules is essential for their reactivity as bifunctional catalysts [12]. Four low-energy conformers were identified with NMR spectroscopy and computational techniques and shown to be interrelated by rotations about the C4′–C9 and C9–C8 bonds (Figure 6.4) [13, 14].

According to molecular modeling (MM) calculations, quinine and quinidine preferentially adopt the *syn*-closed conformation in the gas phase (Figure 6.4). In apolar solvents, however, *anti*-open conformations are observed in NMR spectroscopy for both quinine and quinidine [13]. More advanced *ab initio* calculations revealed that the *anti*-open conformer is preferred in apolar solvents, whereas polar solvents favor the two closed conformers, *syn*-closed and *anti*-closed [14]. However, many other factors (such as intermolecular interactions) are likely to influence the complex conformational behavior of cinchona alkaloids in solution. In addition, protonation of the quinuclidine nitrogen atom is reported to hinder rotation about the C4′–C9 and C8–C9 bonds [15].

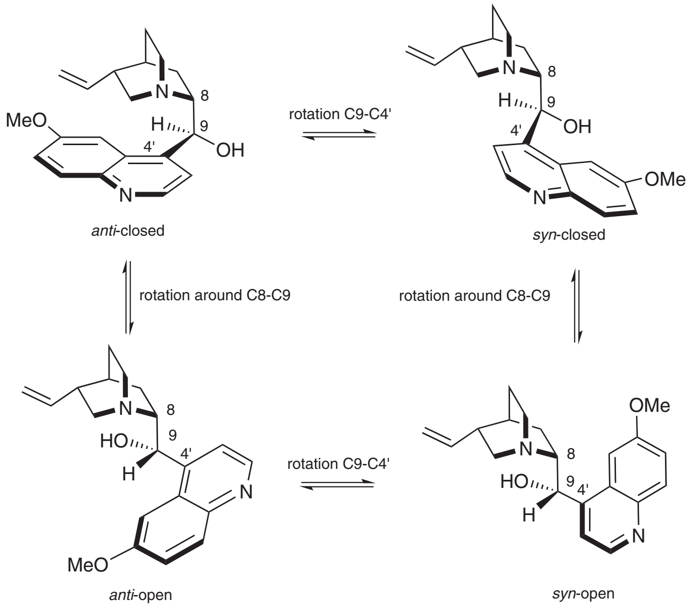
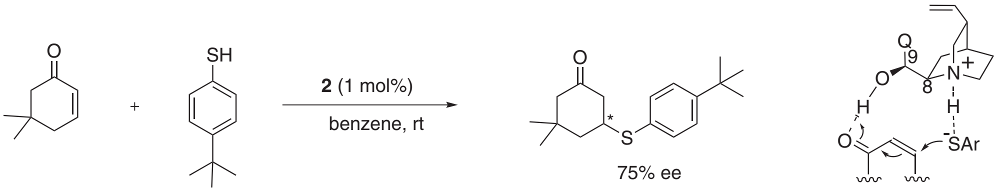


Figure 6.4 The four principal conformers of quinidine.

Substituents at C9 play a key role in determining the conformation of cinchona alkaloids. For example, esters are present in the *anti*-closed form in solution, while C9 methyl ethers prefer an *anti*-open conformation. Recently, the conformations of cinchona alkaloids with a CF_3 and a hydroxyl group at the C9 position were examined with ^{19}F NMR spectroscopy [16]. The CF_3 group was observed to act as a conformational stabilizer by decreasing the rate of rotation around the C4′–C9, thus allowing the *syn* and *anti* conformers to be differentiated at room temperature. The *anti* conformer was observed to be stabilized by polar solvents with the exception of D_2O, in which the *syn* conformer appeared to be preferred. As found for natural cinchona alkaloids, the *syn* conformer dominates in apolar solvents.

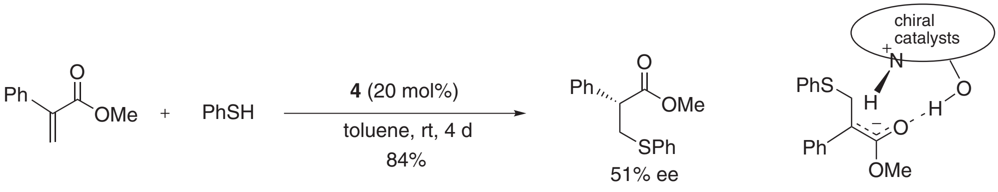
6.3.2
Catalysis with Natural Cinchona Alkaloids

In the early studies of the conjugate addition of aromatic thiols to α,β-unsaturated cyclohexenones, cinchonidine **2** gave the best enantioselectivity (Scheme 6.1), while somewhat lower ee’s were obtained with quinine **1** or quinidine **4** [9]. The mechanistic model advanced in these studies involved activation of the thiol by proton transfer to the nitrogen atom of the quinuclidine moiety and hydrogen bonding between the hydroxyl group at the C9 and the carbonyl group of the unsaturated substrate (Scheme 6.1).



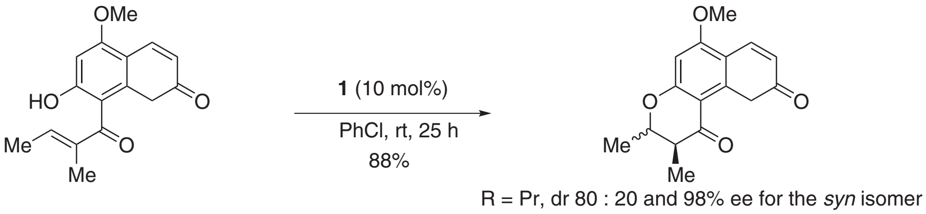
Scheme 6.1 Quinoline is indicated as Q.

Catalysts **1** and **4** are reported to give the best results for the conjugate addition of thiophenol to 2-phenylacrylates (Scheme 6.2) [17]. The products were obtained with opposite enantioselectivity in the reaction with **1** and **4**, respectively, as the catalyst. Based upon a computational analysis, it was proposed that the transition state for the reaction involves hydrogen bonding between the hydroxy group of the catalyst and the carbonyl group of the ester and asymmetric proton transfer from the thiol to enolate anion (Scheme 6.2).



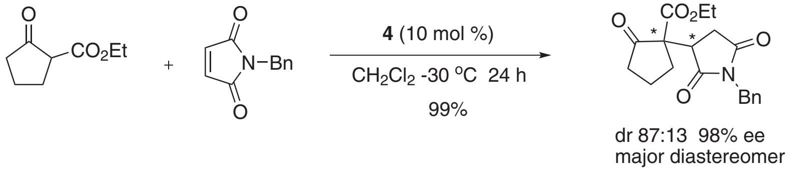
Scheme 6.2

Alkaloid **1** also catalyzed the asymmetric intramolecular oxo-Michael addition of *o*-tigloylphenol in chlorobenzene, leading to *cis*-2,3-dimethyl-4-chromanone (Scheme 6.3) [18], a valuable intermediate in the total synthesis of (+)-calanolide A and (+)-inophyllum B.



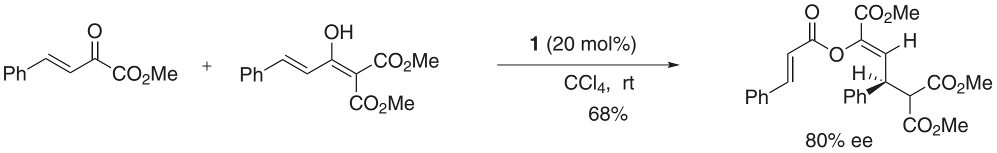
Scheme 6.3

In recent years, various studies were reported on the asymmetric conjugate addition of nucleophiles to unsaturated compounds as catalyzed by natural cinchona alkaloids [3]. For example, conjugate addition of 1,3-dicarbonyl compounds to maleimide or *N*-benzylmaleimide with enantioselective formation of functionalized products with two adjacent stereogenic carbon atoms proved to be catalyzed efficiently by **1** and **4** (Scheme 6.4) [19].



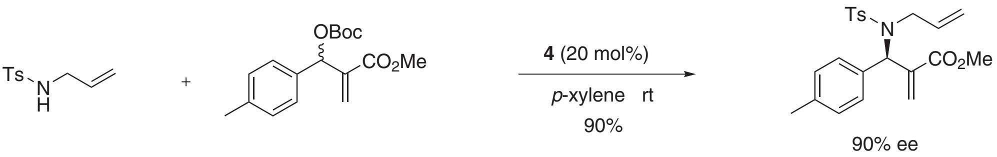
Scheme 6.4

The natural cinchona alkaloids were shown also to catalyze conjugate addition followed by an oxa-nucleophilic rearrangement in the reaction of 2-(1-hydroxy-3-arylallylidene)malonates with β,γ-unsaturated α-ketoesters (Scheme 6.5) [20]. Alkaloid **1** gave the best yields and enantioselectivities compared to other natural cinchona alkaloids and C9 ethers derivatives while a C9 phenyl substituted derivative of quinine appeared to be unreactive.



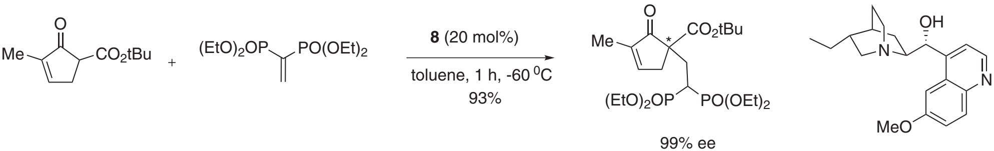
Scheme 6.5

Recently, **4** was reported to be an excellent catalyst for the enantioselective substitution of Morita–Baylis–Hillman carbonates with allylamines [21]. Only carbonates with an aromatic group gave the desired enantioenriched *N*-allyl-β-amino-methylene esters (Scheme 6.6). Ring-closing metathesis of the products of the allylation reaction was shown to result in chiral 2,5-dihydropyroles of importance as starting materials for the synthesis of products of biological and medical interest.



Scheme 6.6

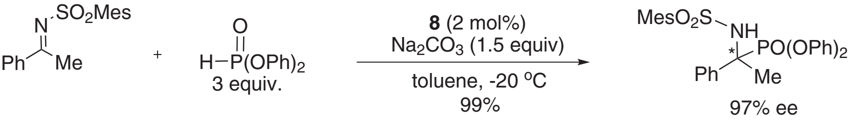
The natural dihydro cinchona alkaloids with the vinyl group reduced to an ethyl group are readily available and frequently included in screening for the most suitable catalysts for a given reaction. Mostly, the reactivity of the dihydro species is similar to that of the parent compounds. For example, in the reaction of 4-*tert*-butylthiophenol with 5,5-dimethylcyclohex-2-enone, an ee of 44% was obtained with dihydroquinidine (**7**) as the catalyst while **4** gave rise to an ee of 55% (see also Scheme 6.1) [9]. In the conjugate addition of cyclic β-ketoesters to ethylidene-bisphosphonate esters, dihydroquinine **8** was observed to lead to the optically active geminal bisphosphonates in high yield and excellent enantioselectively (Scheme 6.7) [22].



8

Scheme 6.7

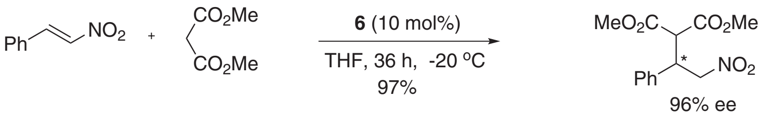
Catalyst **8** was also reported to be suitable for the enantioselective hydrophosphonylation of ketimines (Scheme 6.8) [23] and the asymmetric conjugate addition of diarylphosphane oxides to *trans*-chalcones, affording adducts in up to 89% ee [24].



Scheme 6.8

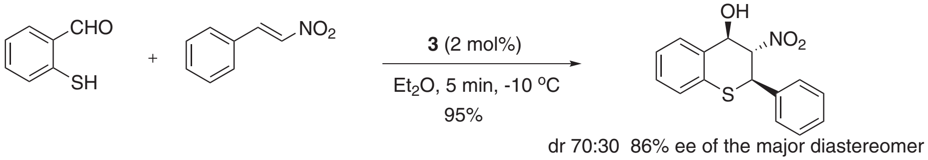
6.3.3
Catalysis with Cupreine and Cupreidine

The phenolic versions of the natural cinchona alkaloids, cupreine **3** and cupreidine **6** (Figure 6.1), are powerful enantioselective catalysts, as detailed in a review [3b]. The usefulness of **3** and **6** was demonstrated by Deng and coworkers in a study of the enantioselective conjugate addition of malonates to nitroalkenes (Scheme 6.9) [25]. Higher enantioselectivities and rates were obtained with **6** than with **4**, indicating that the aromatic-OH and the quinuclidine nitrogen are both important for catalysis of the conjugate addition to nitroalkenes.

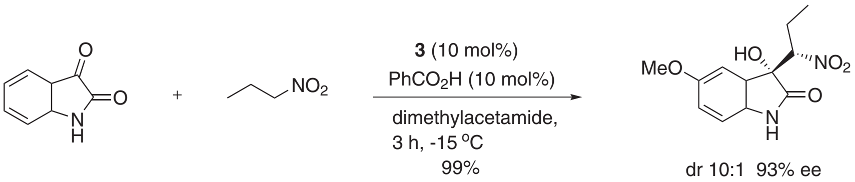


Scheme 6.9

The derivatives **3** and **6** without any additional modification at the C9 position are infrequently used for organocatalysis. Recent examples include the synthesis of enantioenriched 1,3,4-trisubstituted thiochromanes by a tandem conjugate addition–Henry reaction between 2-thio-substituted benzaldehydes and nitrostyrenes (Scheme 6.10) [26] and the Henry reaction between isatin and simple nitroalkanes to form 3-substituted 3-hydro-oxindoles (Scheme 6.11) [27].

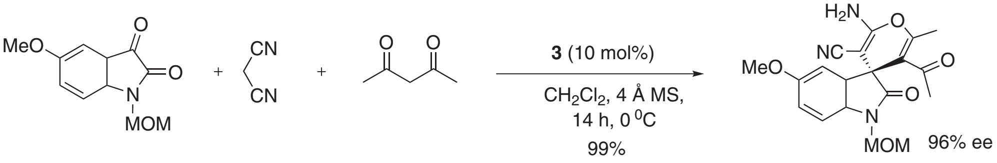


Scheme 6.10



Scheme 6.11

Catalyst **3** was also used in the construction of substituted 3-hydroxy-2-oxindoles by the reaction of 5-methoxy substituted isatins with various indoles [28]. Up to 91% ee could be obtained in 1,4-dioxane as the solvent and benzoic acid as an additive. Similarly, **3** was applied as catalyst for the formation of spiro[4*H*-pyran-3,3′-oxindoles] via a one-pot domino Knoevenagel, conjugate addition, cyclization sequence (Scheme 6.12) [29].



Scheme 6.12

6.4
Cinchona Alkaloids with an Ether or Ester Group at C9

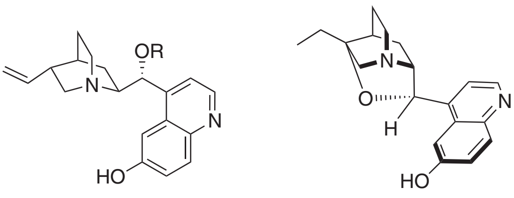
6.4.1
Structural Properties

Conversion of the -OH group at C9 into a simple ether or ester function is straightforward and eliminates evidently the possibility for the catalysts to activate an electrophile through hydrogen bonding. Functionalization at C9, therefore, is mostly performed in combination with transformation of the C6′ methoxy group into another group, for example, a simple hydroxyl group [3, 25], thus leading to derivatives of **3** and **6** (Figure 6.5). A pertinent example of this class of cinchona alkaloid derivatives is the so-called β-isocupreidine **12** (an oxazatwistane) with an intramolecular ether bridge between C9 and C3 (Figure 6.5) [30, 31]. β-Isocupreidine can be obtained as described by Hoffmann [31] and by Hatakeyama and coworkers, who also devised a synthesis for the pseudo-enantiomer of this cinchona alkaloid derivative [32, 33]. The intramolecular ether linkage in **12** restricts the conformational flexibility of the molecule and induces a preference for a *gauche* open structure (Figure 6.5) [34].

6.4.2
Catalysis with C9 Ethers of Natural Cinchona Alkaloids

The simple C9 ethers derived from the natural cinchona alkaloids are infrequently applied in organocatalysis. A relatively recent example concerns an asymmetric cyclopropanation reaction with the C9 *O*-methyl derivatives of **1** and **4**, respectively (Scheme 6.13) [35]. The functionalized cyclopropanes were obtained in excellent diastereo- and enantioselectivity as well as in high yields.

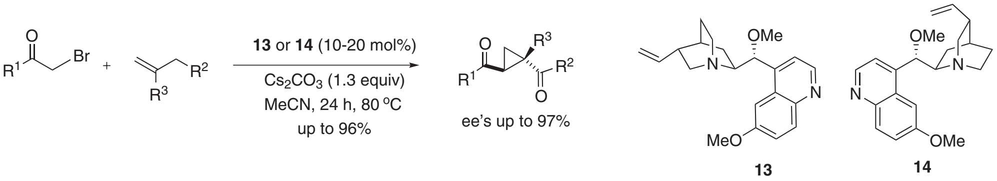
In a subsequent study, it was observed that the introduction of an additional methyl group at the C2′ of the quinoline ring in **13** or **14** results in an excellent catalyst for an intramolecular version of the reaction leading to bicyclo[0.1.4]heptanes as single diastereomers (Scheme 6.14) [36].



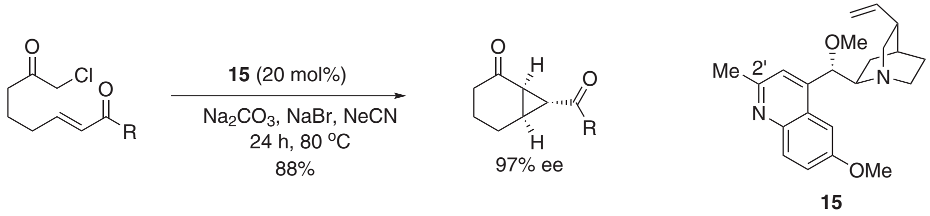
9 R = *n*-Bu
10 R = Bn
11 R = phenanthryl

12

Figure 6.5 C9 ether derivatives of cupreine and cupreidine.

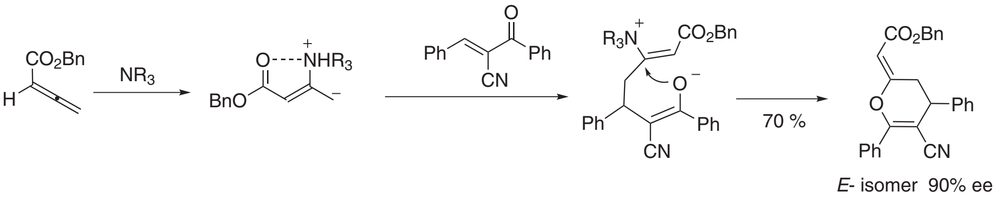


Scheme 6.13 Formation of cyclopropanes [R^1 = OBu^t, NEt_2, NMe(OMe), R^2 = Aryl, alkyl, OR, R^3 = H, Me, $NHBoc_2$].



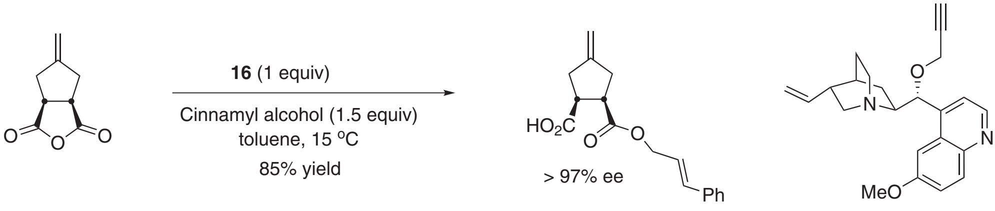
Scheme 6.14

Recently, **13** was reported to catalyze the asymmetric annulation reaction between allenoates and α,β-unsaturated carbonyl compounds to form substituted 2*H*-pyrans (Scheme 6.15) [37]. This formal [4+2] cycloaddition afforded exclusively the product with the (*E*) configuration of the *exo*cyclic double bond, in line with calculations that indicated the (*E*)-isomer to be about 14.2 kJ mol^{-1} lower in energy than the (*Z*) isomer. The mechanism of the reaction was formulated as an initial attack by the nitrogen atom of the quinuclidine ring at the allenoate with formation of an ionic intermediate that preferentially reacts at the terminal carbon atom with the α,β-unsaturated carbonyl compound prior to elimination of the catalyst with formation of the 2*H*-pyran derivative (Scheme 6.15).



Scheme 6.15 Asymmetric annulation reaction catalyzed by **13** (NR_3 in the scheme).

Cinchona alkaloid derivatives are rarely applied in large-scale preparations of enantioenriched compounds. One example, though, is the large-scale enantioselective desymmetrization of *meso*-anhydrides (Scheme 6.16) as catalyzed by the C9 *O*-propargyl ethers of **1** and **4** [38].



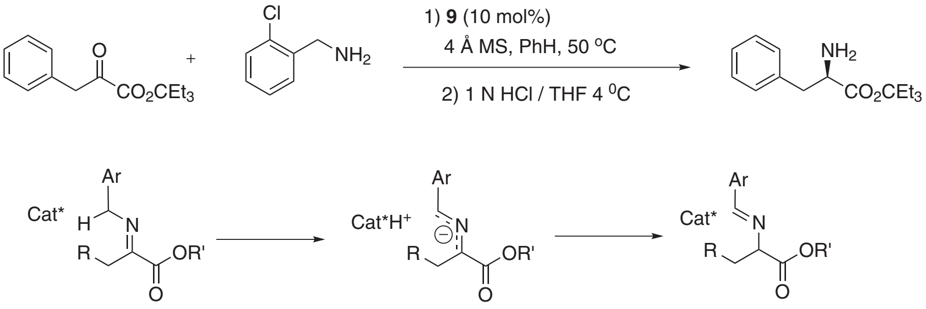
16

Scheme 6.16

6.4.3

Catalysis with C9 Ethers of Cupreine and Cupreidine

Recently, **9** (Figure 6.5) was shown to catalyze the biomimetic transformation of α-keto esters to α-amino acids with various functional groups [39]. The reaction is pictured in Scheme 6.17 as involving imine isomerization catalyzed by **9** prior to hydrolysis and the favored formation of the α-amino ester in the (*R*) configuration. Various phenylalanine derivatives could be obtained by this reaction. The reaction worked equally well for α-keto esters with an aromatic or aliphatic group and for esters with an ether or thioether function in addition to the α-carbonyl group.



Scheme 6.17

The importance of an -OH group at the C6′ position for an organocatalytic reaction was noted by Deng and coworkers in a series of studies of C9 ether derivatives of cupreine and cupreidine [34]. Based on the observation that the C9 *O*-benzyl and *O*-phenanthryl ether derivatives (**10** and **11**, respectively, Figure 6.5) gave similar results for the conjugate addition of carbon nucleophiles to nitroalkenes as obtained with **3** (Scheme 6.18) [34], a transition state model was proposed for this reaction.

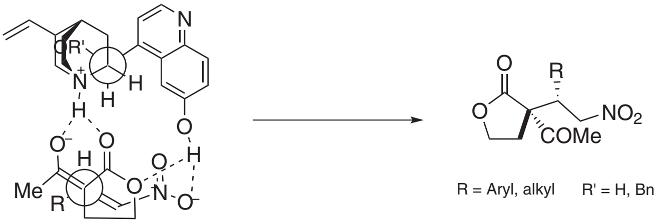
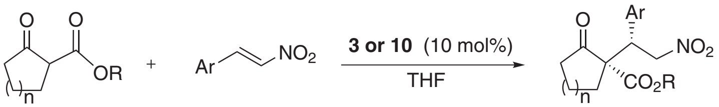


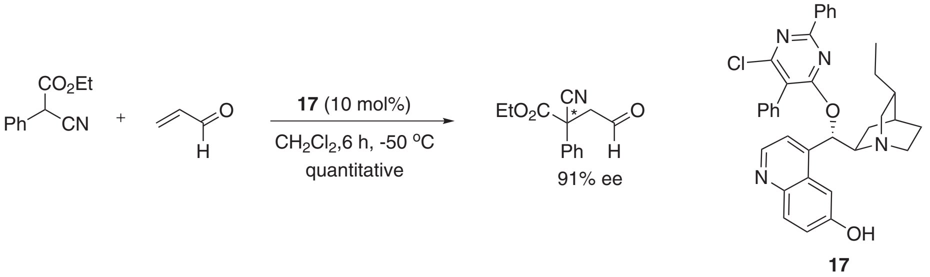
Figure 6.6 Tentative model for the transition state of the catalytic conjugate addition of a carbon nucleophile to a nitroalkene with the cupreine derivative in a gauche open conformation [34].



Scheme 6.18 With **3:** *n* = 2, R = Et, Ar = 4-Br-C$_6$H$_4$-, −20 °C, dr > 98: 2 and 99% ee. With **10:** *n* = 1, R = Me, Ar = Ph, −60 °C, dr 94:6 and >99% ee.

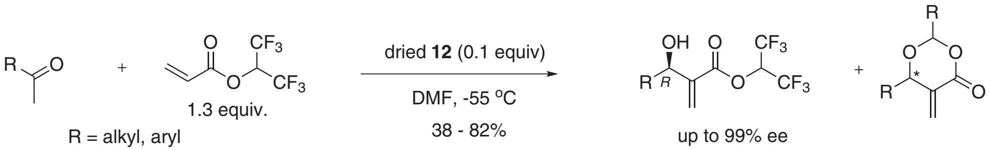
In the transition state model proposed for this reaction (Figure 6.6), the catalyst adopts a *gauche* open conformation in order to activate the electrophile by hydrogen bonding involving the C6′ OH group. In addition, hydrogen bonding involving the nitrogen atom of the quinuclidine ensures the right position of the reactants prior to bond formation between the reactant carbon atoms in a staggered arrangement. A comparable transition state structure was advanced in a recent study of the formation of tetrahydroindane derivatives with four stereocenters by sequential conjugate additions between cyclic γ,δ-unsaturated-β-ketoesters and nitroalkanes catalyzed by **10** [40].

In subsequent studies by Deng [41, 42] and others [43], the C9 *O*-phenanthryl derivatives of cupreine **11** and cupreidine were found to be highly efficient and stereoselective catalysts. In the reaction of α-substituted β-ketoesters with α,β-unsaturated ketones, high yields and enantioselectivities (up to 99%) were obtained with the phenanthryl derivatives and a catalyst loading of 1–10 mol% [41]. Comparable findings were reported for the reaction with acrolein, whereas different C6′ OH cinchona alkaloids failed to give satisfactory ee's for the conjugate addition of α-phenyl α-cyanoacetate to acrolein [42]. However, the introduction of a 4-chloro-2,5-diphenylpyrimidinyl group at the C9 oxygen atom in dihydrocupreidine **17** was discovered to improve the catalytic activity [41b]. As a result, the products were formed in a much higher enantioselectivity than, for example, with **10** (Scheme 6.19).



Scheme 6.19

The β-isocupreidine **12**, a structurally unique member of this class of cinchona alkaloid derivatives (Figure 6.5), was shown to be an appropriate catalyst for a large number of organic reactions. In particular, the Morita–Baylis–Hillman reaction was subjected to catalysis with **12**, as first reported by Hatakeyama and coworkers for the highly enantioselective reaction of hexafluoroisopropyl acrylate with various aldehydes [32] and in ensuing work with imines [44] or chiral *N*-Boc-α-amino aldehydes as the substrates [45]. The reaction with aldehydes yielded the desired Morita–Baylis–Hillman products in good to excellent ee's, albeit only in moderate yields owing to the formation of a substituted dioxanone as byproduct (Scheme 6.20).



Scheme 6.20

The α-methylene-β-hydroxy esters were obtained in the (*R*) configuration and the dioxanone in the (*S*) configuration, whereas the reaction with aromatic imines led to (*S*)-enriched *N*-protected-α-methylene-β-amino acid esters [44]. The mechanistic proposal for the reaction with imines, as shown in Figure 6.7, indicates more steric interaction in intermediate B than in intermediate A. As a result, intermediate A reacts to form the Morita–Baylis–Hillman product, whereas intermediate B prefers to redissociate into reactants. The difference in the rate of the elimination step of the two intermediates leads to the preference for the (*S*) configuration through equilibration between intermediates A and B.

The derivative **12** was also applied successfully in the reaction of racemic Baylis–Hillman carbonates with cyanoesters [46], in the preparation of a 3-hydroxy-2-methylene-pentanoate as a starting material for the formal total synthesis of

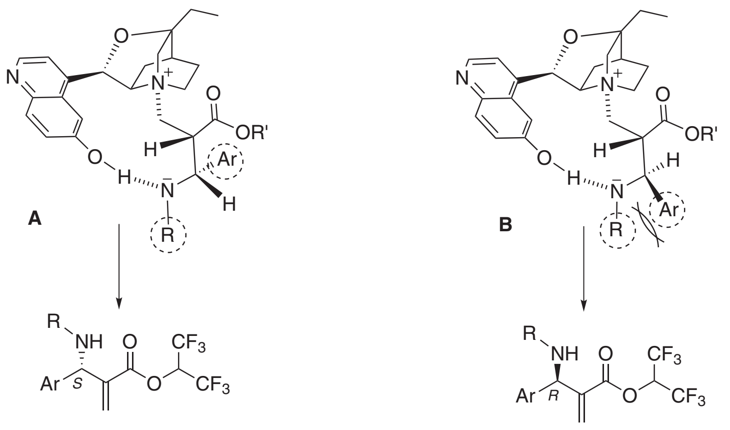
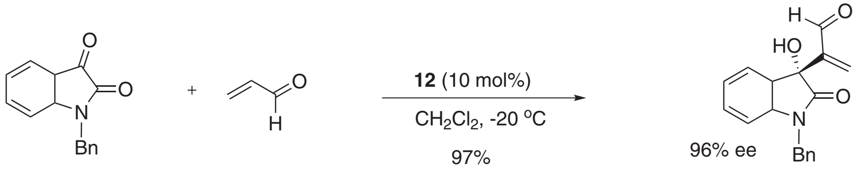


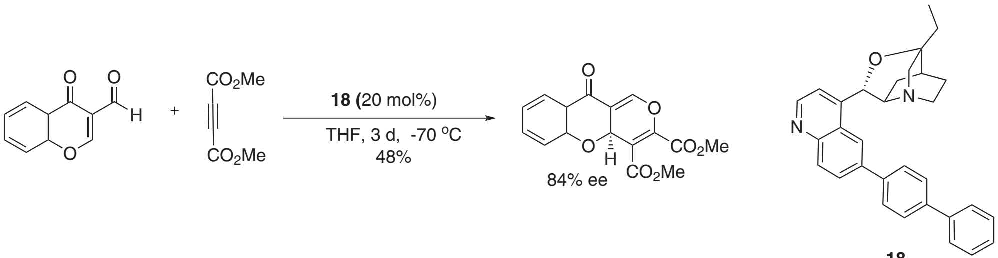
Figure 6.7 Tentative and simplified intermediate structures formed in the reaction of imines, ArCH=NR, with hexafluoroisopropyl acrylate, R = Ar, Bz, Ms, Ts, P(O)Ph_2 and R = $CH(CF_3)_2$ [44]. The best results were obtained with R = P(O)Ph_2 (yields up to 97% and ee up to 73% prior to recrystallization).

(+)-fostriecin and (+)-phoslactomycin B [47], in the aza-Morita–Baylis–Hillman reaction of *N*-tosyl salicaldehyde imines with α,β-unsaturated ketones [48], and in the asymmetric synthesis of 3-hydroxy-2-oxindoles [49, 50]. In the latter reaction, *N*-methyl or *N*-benzyl protected isatins were reacted with acrolein in CH_2Cl_2 to afford the substituted indoles in high yields and enantioselectivity (Scheme 6.21). Ethyl acrylate reacted slowly with *N*-benzyl-protected 5,7-dibromo substituted isatin in CH_2Cl_2 [49] to give the substituted indole in 50% isolated yield and 96% ee. In a parallel study by Lu and coworkers [50], however, **12** was shown to catalyze the Morita–Baylis–Hillman reaction between isatins and acrylates relatively efficiently (24–72 h at room temperature) in THF or $CHCl_3$, giving the products in high yields (up to 96%) and excellent ee (up to 96%).



Scheme 6.21

In addition, **12** was reported to be a suitable organocatalyst for other reactions, including amination of α-cyanoacetates or β-carbonyl esters by reaction with azodicarboxylate followed by nitrogen-nitrogen bond cleavage of the resultant hydrazine [51]. Recently, a β-isocupreidine with a biphenyl group at C6′ instead of a hydroxyl functionality was reported to catalyze the enantioselective [4+2] annulation of substituted chromone-3-carbaldehydes and related imines (Scheme 6.22) [52].



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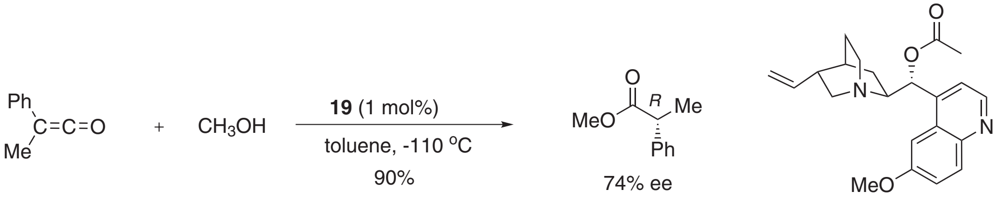
Scheme 6.22

6.4.4
Catalysis with C9 Esters

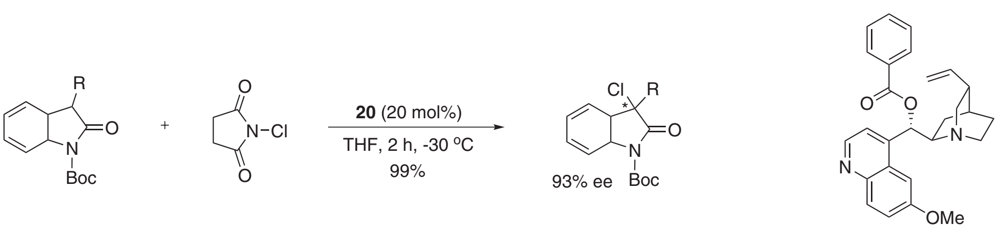
In pioneering studies by Pracejus, C9 *O*-acetylquinine **19** was observed to catalyze the addition of methanol to phenyl methyl ketene (Scheme 6.23). Nucleophilic attack of the nitrogen atom of the quinuclidine was rate determining and was followed by an asymmetric protonation step [7].



19

Scheme 6.23

A recent example with a benzoyl derivative is provided by the asymmetric chlorination of 3-aryl-*N*-Boc-oxindoles with *N*-chlorosuccinimide as the chlorine source and C9 *O*-benzyl quinidine **20** as catalyst (Scheme 6.24) [53]. Comparably, benzoyl esters of quinine were applied with metal-containing Lewis acids as co-catalysts for enantioselective [4+2] cycloadditions – for example, the addition of ketene enolates to ortho-quinone [54].



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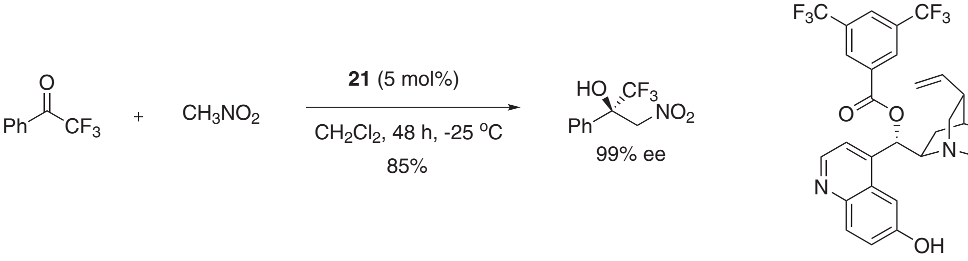
Scheme 6.24

With respect to cupreidine, C9 *O*-benzoyl esters of this cinchona derivative were demonstrated to be the best catalysts for the nitroaldol reaction of α-ketoesters [55], the conjugate addition of anthrone to nitroalkenes [56], the Henry reaction with fluoromethyl ketones (Scheme 6.25) [57], and an aza-Friedel–Crafts reaction of naphthols with *N*-sulfonyl imines [58].



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Scheme 6.25

6.5
Cinchona Alkaloid Derivatives with a Sulfonamide, Urea, Thiourea, Squaramide, or Guanidine Function

6.5.1
Structural Properties

The concept of bifunctional catalysis as advanced for the natural cinchona alkaloids and cuprei(di)nes has resulted in the design and synthesis of a range of new cinchona derivatives. The major part of these novel organocatalysts are urea and thiourea cinchona derivatives together with cinchona alkaloids modified with, for example, a sulfonamide, squaramide, or guanidine group (Figure 6.8).

The different functional groups in Figure 6.8 can activate an electrophile by double hydrogen bonding as indicated in Figure 6.9, in which a urea or thiourea group coordinates to the carbonyl group of the substrate while the nitrogen atom of the quinuclidine interacts with the nucleophile. The strength of the interaction with the electrophile will clearly depend on the distance between the hydrogen

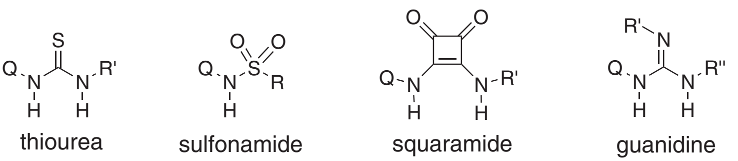


Figure 6.8 Functionalities incorporated in cinchona-based organocatalysts (Q represents the chiral cinchona part of the catalyst).

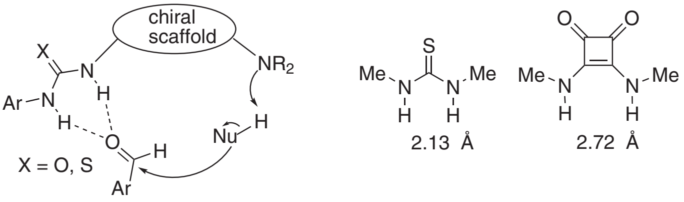


Figure 6.9 Electrophile activation by double hydrogen bonding.

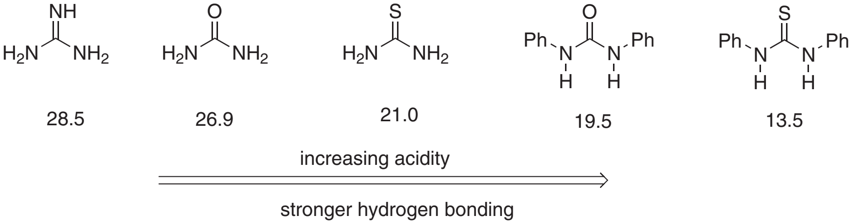
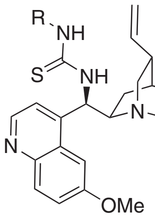


Figure 6.10 pK_a values in DMSO as solvent.

atoms on the two nitrogen atoms and the acidity of this group within a series of closely related species. As indicated in Figure 6.9, the calculated distance between the hydrogen atoms in *N,N*-dimethylthiourea is 2.13 Å (a similar distance can be expected for the related urea and quinidine species) and in the *N,N*-dimethylsquaramide the distance is 2.72 Å [59]. Irrespective of the somewhat larger distance in the squaramide than in the thiourea, cinchona derivatives with a squaramide group have been shown to be effective and enantioselective organocatalysts (Section 6.6.2).

With respect to acidity, an increase in acidity of the N–H entities is expected to lead to stronger hydrogen bonding [60, 61]. As shown in Figure 6.10, a thiourea is considerably more acidic than the related urea species and thus also more effective in undergoing hydrogen bonding with an electrophilic reactant. The values refer to simple compounds but clearly show a significant increase in acidity upon introduction of phenyl groups.

For cinchona alkaloids modified with one of the functionalities in Figure 6.10 few data are available. In a recent study, however, by Cheng, Lou, and coworkers [62] the acidity in DMSO of a series of thiourea-based organocatalysts were measured, including five cinchona derivatives with this functionality at the C9 position (Figure 6.11). The thiourea compound with an aliphatic R group is the weakest acid of the series, with a pK_a slightly lower than that of thiourea itself. For the four thioureas with an aromatic group, the acidity increases in agreement with the nature of the substituents, with the 3,5-$(CF_3)_2C_6H_3$-containing cinchona derivative being the most acidic. For the conjugate addition of malonates to nitrostyrene as catalyzed by the four thioureas with an aromatic group, the rate and enantioselectivity were observed to increase with an increase in acidity. However, the thiourea



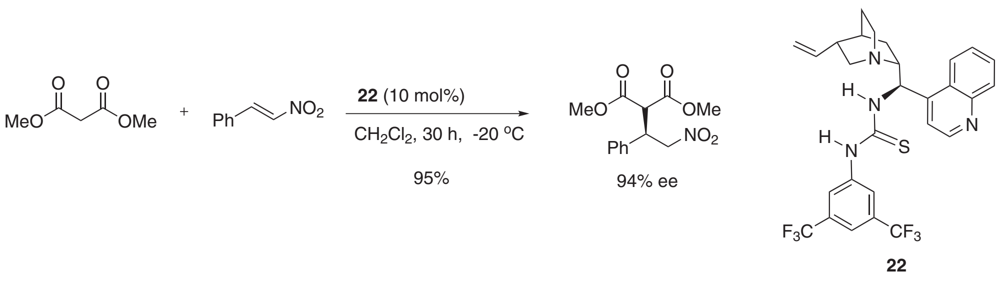
R	pK_a
R = 4-MeC$_6$H$_4$	pK_a = 16.2
R = Ph	pK_a = 15.8
R = 4ClC$_6$H$_4$	pK_a = 15,2
R = 3,.5-(CF$_3$)$_2$C$_6$H$_3$	pK_a = 13.2
R = *n*-Bu	*pK*$_a$ = 19.5

Figure 6.11 pK_a values of thiourea derivates in DMSO.

derivative with an aliphatic group gave rise to a higher rate and enantioselectivity than predicted solely on the basis of acidity, indicating that factors other than the pK_a of the thiourea influence the catalytic properties of the cinchona alkaloid derivatives [62].

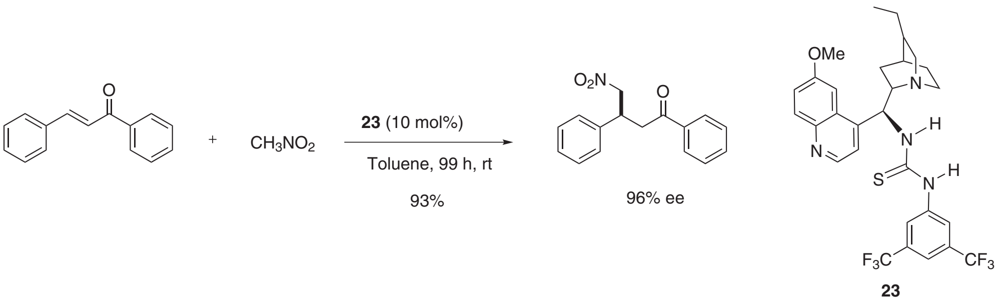
6.5.2
Catalysis with C9 and C6′ Thiourea Derivatives

The modification of cinchona alkaloids by substituting the C9–OH for a thiourea group was motivated by a series of studies on the development of organocatalysts with this particular functionality by Jacobsen and coworkers [63] as well by the group of Takemoto [64]. These first studies revealed that synthetic (thio)ureas of organic compounds can be effective and enantioselective catalysts. Inspired by these reports, several groups prepared cinchona alkaloids with a (thio)urea group and examined their applicability as enantioselective catalysts. In the first report by Chen and coworkers [65], the C9 thiourea substituted epicinchonine and epicinchonidine were found to be effective catalysts for the conjugate addition of arylthiols to α,β-unsaturated imides even though the products were obtained in low enantioselectivity. In a concurrent study by Dixon and coworkers, the epi form of the C9 thiourea-substituted cinchonine **22** was observed to catalyze the conjugate addition of malonates to nitroalkenes with the formation of products in high yields and enantioselectivity (Scheme 6.26) [66].



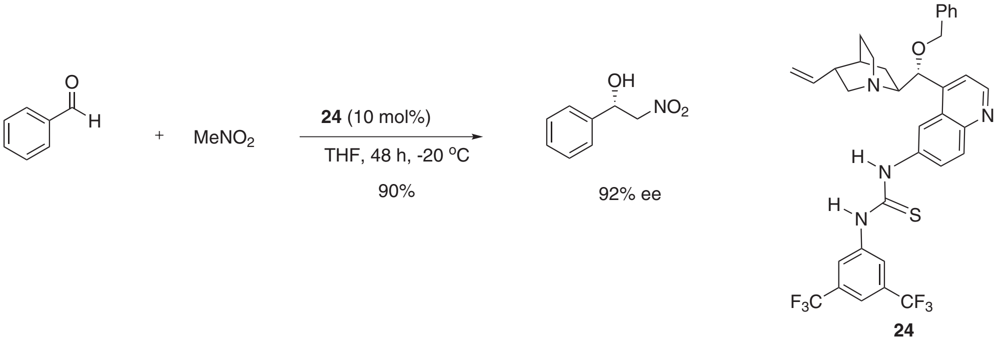
Scheme 6.26

Soós and coworkers were the first to report the development of C9 thiourea-substituted organocatalysts based on **1** and **4** [67]. They examined the conjugate addition of nitromethane to chalcones and obtained poor results for **1** and no catalytic activity with epiquinine. The thiourea obtained from **1** and with the natural configuration at C9 also showed no catalytic activity in the reaction of nitromethane with chalcones. However, the epi form of the C9 thiourea from quinine furnished the products in a good yield and high enantioselectivity (Scheme 6.27) and a further improvement in yield and enantioselectivity was obtained with the dihydro-thiourea derivative of epiquinine **23.** Similar findings were reported independently by Connon and coworkers, who discovered that the C9 thiourea derivatives of dihydroquinine or dihydroquinidine in the epi form proved to be excellent catalysts for the conjugate addition of malonates to unsaturated nitro compounds [68].



Scheme 6.27

Functionalization of the cinchona structure with a thiourea at the C6′ position of the quinolone ring was demonstrated shortly after development of the C9 derivatives [69]. The transformation of the C6′ methoxy group into a thiourea bearing a 3,5-di(trifluoromethyl)phenyl group, without affecting the stereochemistry at C9, resulted in a highly effective organocatalyst for the asymmetric Henry reaction of nitromethane with aromatic aldehydes (Scheme 6.28).



Scheme 6.28

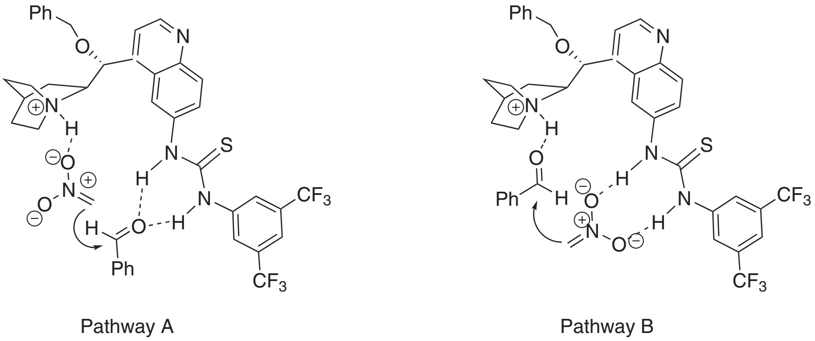
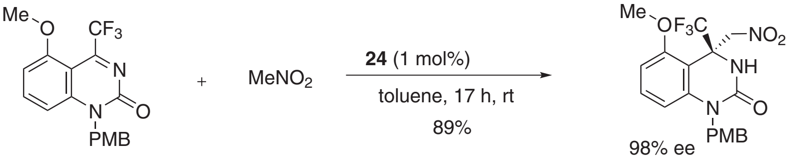


Figure 6.12 Simplified intermediate structures in the Henry reaction.

An ensuing computational study of the thiourea-catalyzed Henry reaction indicated that the both substrates are activated simultaneously in two ways; that is, the thiourea can interact either with the aldehyde (pathway A) or with the nucleophile (pathway B) (Figure 6.12) [70]. The computed reaction barriers for the bond-forming steps in the two pathways differed by less than 8 kJ mol^{-1} and therefore both could be important under the experimental conditions for the catalytic Henry reaction.

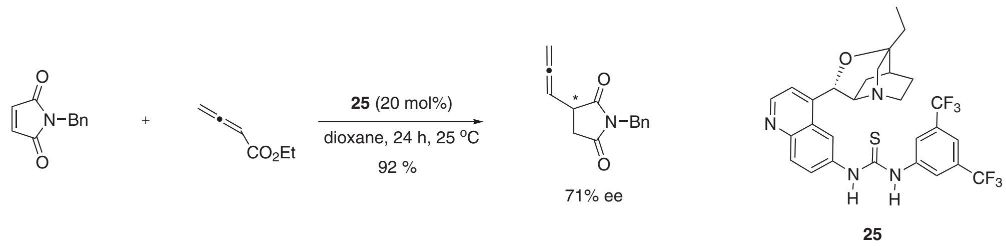
The C6′ thiourea **24** has been shown recently to be well suited for the enantioselective aza-Henry reaction of nitromethane with ketimines, yielding the products in high yields and ee's (Scheme 6.29) [71]. The reaction was also performed with a nitro-cyclopropane alkane and a trifluoromethyl substituted ketamine, thus forming a precursor for the synthesis of possible anti-HIV drug candidates.



Scheme 6.29

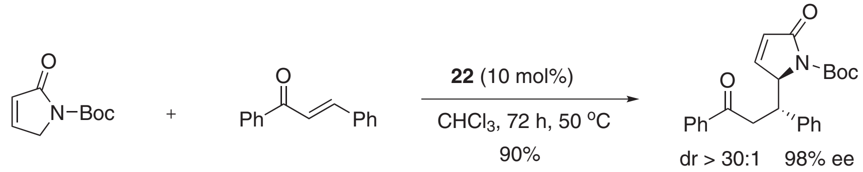
In addition, a C6′ thiourea derivative of β-isocupreidine **25** has been prepared and shown to catalyze the Rauhut–Currier reaction between allenoates and maleimides with the formation of products in a high yield but only moderate ee (Scheme 6.30) [72].

The C9 thiourea derivative **23** [67] was applied in a plethora of organic reactions. Much of this research has been reviewed elsewhere (see, for example, References [3e,g,i,j]) and demonstrates the outstanding potential and versatility of thiourea-derived cinchona alkaloids for organocatalysis. Recently, several studies were concerned with conjugate additions catalyzed by C9 thiourea derivatives. For example,



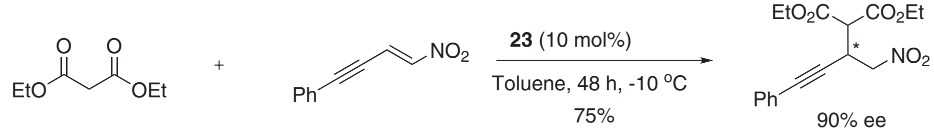
Scheme 6.30

Wang and coworkers reported high yields and enantioselectivity for the conjugate addition of α,β-unsaturated-γ-butyrolactam to chalcones (Scheme 6.31) as catalyzed **22** [73].

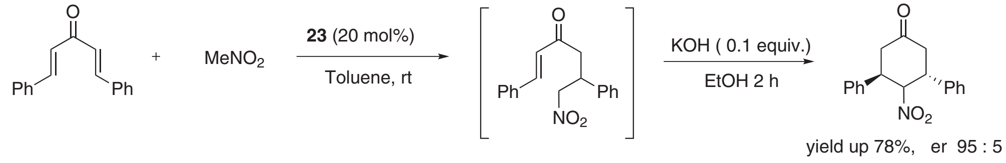


Scheme 6.31

The conjugate addition of aromatic and aliphatic α-nitro-ketones to α,β-unsaturated-α-keto esters was also reported to be catalyzed efficiently and with moderate to high enantioselectivity by **23** [74]. In addition, **23** appeared to catalyze the enantioselective conjugate addition of malonates to nitroenynes to furnish chiral β-alkynyl esters (Scheme 6.32) [75]. In a recent study, **23** was shown to catalyze the formation of chiral 4-nitro-cyclohexanones via a double conjugate addition reaction of nitromethane to dienones (Scheme 6.33) [76].

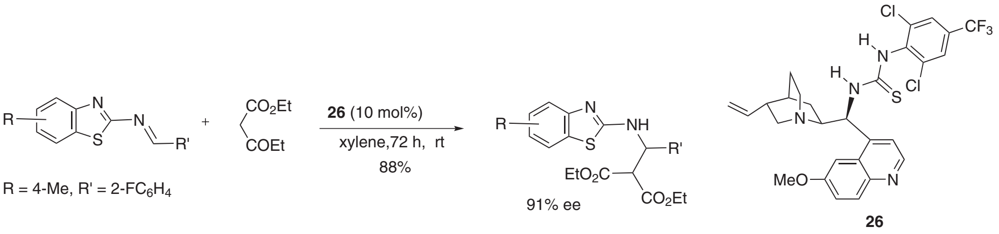


Scheme 6.32



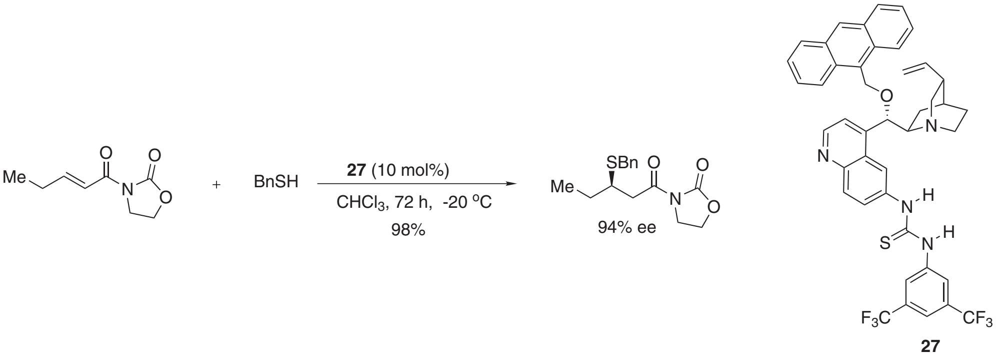
Scheme 6.33

Cinchona alkaloids with a thiourea group have also been applied for the asymmetric preparation of amino acid derivatives. Recent examples include an asymmetric Mannich reaction leading to β-amino ester derivatives with a benzoxazole moiety [77] and the formation of β-amino esters with a benzothiazole group [78]. The latter reaction was catalyzed efficiently by a C9 thiourea derivative (**26**) with a 2,6-dichloro-4-(trifluoromethyl)phenyl group connected to the thiourea group as shown in Scheme 6.34.



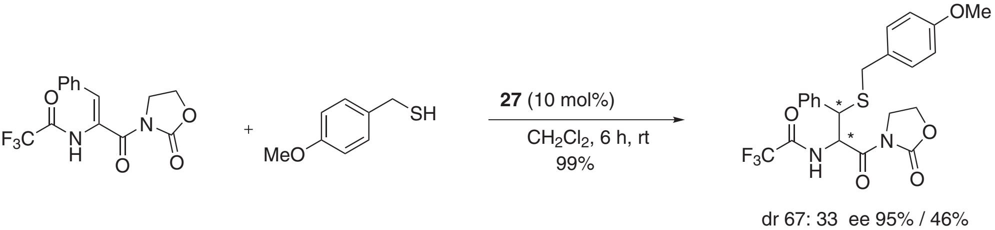
Scheme 6.34

A study by Deng and coworkers demonstrated that the addition of alkanethiols to α,β-unsaturated *N*-acylated oxazolidin-2-ones is catalyzed by a C6′-thiourea substituted cinchona alkaloid **27**, which has a 9-methylanthracyl ether at C9 (Scheme 6.35) [79]. The reaction could be performed with a wide range of alkanethiols and a considerable degree of variations of the unsaturated acceptor. The product of the reaction of 4-methoxybenzyl thiol could subsequently be converted in high yields into a β-thiol ester by removal of the benzylic group and conversion of the oxazolidin-2-one part into an ester.



Scheme 6.35

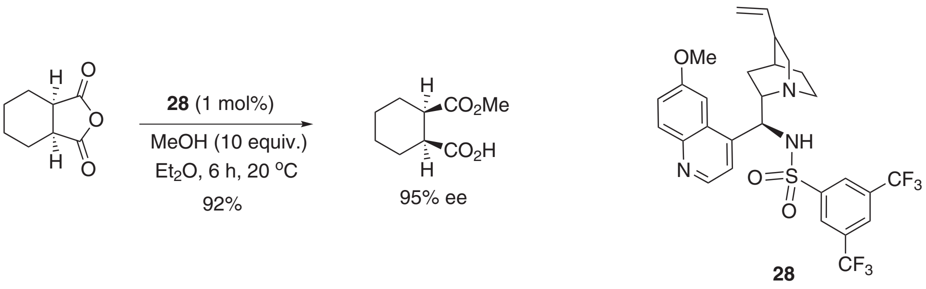
Recently, **27** was applied in the asymmetric conjugate addition of thiols to *N*-acylated oxazolidin-2-one derivatives of α,β-unsaturated amino acids [80]. The products were formed in good yields, with a low to moderate diastereoselectivity and a modest to excellent enantioselectivity for the major diastereomer (Scheme 6.36). Subsequently, the trifluroacetyl could be replaced by an Fmoc group, thus affording β-thiol amino acid derivatives for application in peptidomimetics.



Scheme 6.36

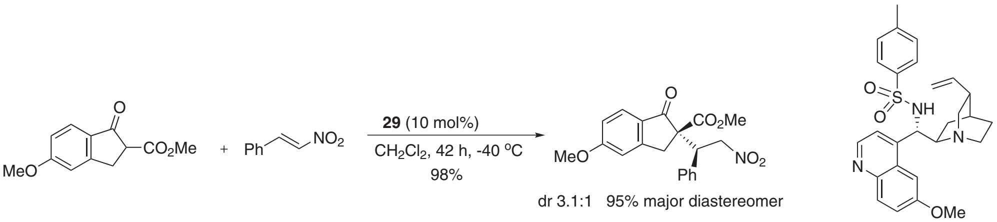
6.5.3
Catalysis with C9 Sulfonamide, Squaramide, and Guanidine Derivatives

In 2008, Song and coworkers introduced a sulfonamide derivative of epiquinine (**28**) as a robust organocatalyst for the desymmetrization of cyclic anhydrides by methanol (Scheme 6.37) [81]. The preference for a sulfonamide over a thiourea group was based on a study that revealed that the formation of hydrogen-bonded dimers (as observed by NMR [82]) of thiourea derivatives influences the reactivity of the catalyst [83]. An increase in ee was observed with (i) a decrease in the concentration of thiourea catalyst related to **28**, (ii) an increase in the temperature, and (iii) solvents capable of accepting hydrogen bonds such as ethers. In contrast to the results for the thiourea analog, no significant effect of concentration and temperature on the catalytic reactivity and enantioselectivity was observed with **28** as catalyst.



Scheme 6.37

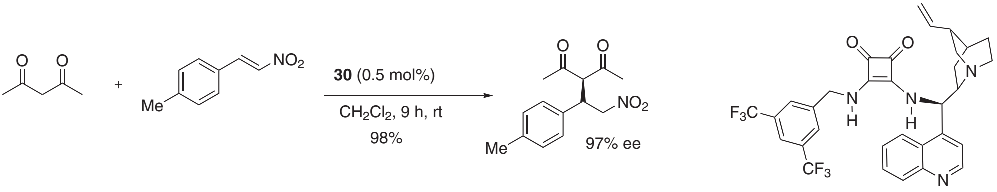
In addition to enantioselective alcoholysis of meso anhydrides [84, 85], a series of sulfonamide derivatives of quinidine was prepared and shown to effectively catalyze the conjugate addition of bicyclic α-substituted β-ketoesters to β-nitroalkenes (Scheme 6.38) [86].



29

Scheme 6.38

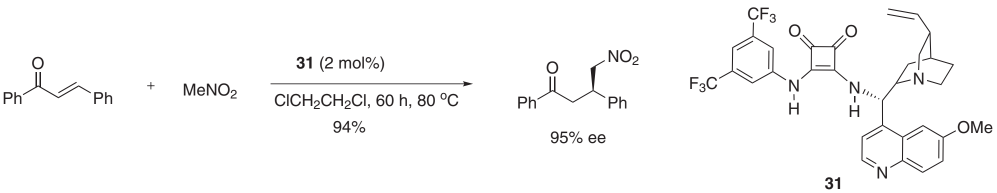
Rawal and coworkers prepared a squaramide derivative of cinchonine (**30**) and proved this cinchona alkaloid analog to be an efficient catalyst for the conjugate addition of 2,4-pentadione to β-nitrostyrene [59] (Scheme 6.39). With substituted 2,4-pentadiones, the diastereoselectivity was low, except for the methyl ester of 2-oxocyclopentanecarboxylic acid, which gave rise to a ratio of 50 : 1 for the diastereoisomers.



30

Scheme 6.39

The C9 squaramide derivatives of quinine (**31**) and quinidine have also been prepared and shown to catalyze the addition of nitromethane to chalcones (Scheme 6.40). Catalysts with a 3,5-$(CF_3)_2C_6H_3$ group attached to the second nitrogen performed slightly better than if a 4-$CF_3C_6H_4$ or 4-FC_6H_4 group was present [87].

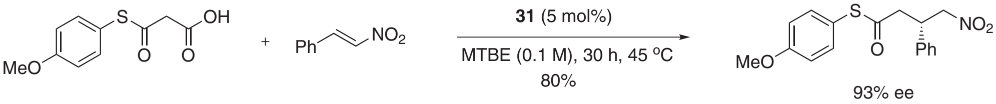


31

Scheme 6.40

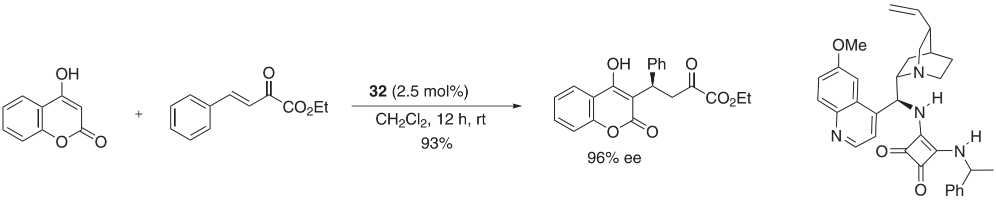
Comparable results were obtained for asymmetric conjugate addition of aromatic and aliphatic thiols to chalcones [88]. For this reaction it was also observed that **31** was a more suitable catalyst than derivatives with, for example, a 4-$CH_3OC_6H_4$, a 3,5-$(CH_3)_2C_6H_3$, or a cyclohexyl group, which is in line with the expectation that the acidity of the squaramide N–H groups is related to the stereoselectivity and yield of the catalytic reaction.

Song and coworkers compared the squaramide **31** with the sulfonamide **28** and the related C9 thiourea derivative as catalyst for the conjugate addition of 1,3-dicarbonyls to β-nitroalkenes in brine [89] and the conjugate addition of malonic acid half thioester to various nitro alkenes [90]. In the latter reaction (Scheme 6.41), **31** afforded the best results with respect to enantioselectivity; that is, the ee was 93% for **31** but only 63% for thiourea and 23% for the sulfonamide analog.



Scheme 6.41

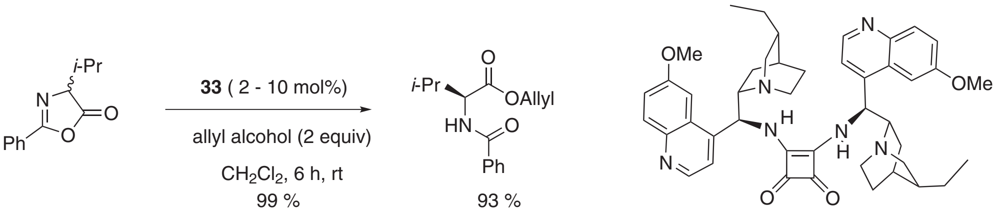
A study by Xu and coworkers examined a series of cinchona alkaloid derivatives with a benzyl or 1-phenylethyl group at the second nitrogen atom of the squaramide moiety [91]. The catalyst with 1-phenylethyl group and a C6′ methoxy group (**32**) gave the highest yield and enantioselectivity for the conjugate addition of 4-hydroxycoumarins to α-keto esters (Scheme 6.42).



32

Scheme 6.42

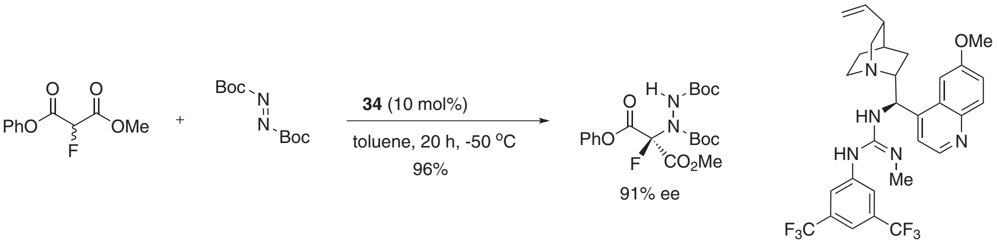
Squaramide-based dimeric cinchona alkaloid organocatalysts have also been described [92] and shown to be highly suitable for the dynamic kinetic resolution of racemic azlactones (Scheme 6.43). The dimeric squaramide derivatives were free from self-association, as indicated by the observation that the enantioselectivity was not influenced to any significant extent by the concentration of the dimeric squaramide, in contrast to the monomeric species that showed a decline in ee upon an increase in concentration.



33

Scheme 6.43

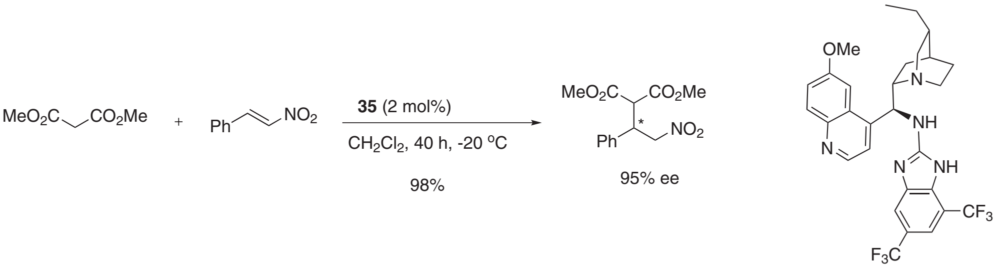
Cinchona-based organocatalysts with a guanidine functionality were studied by Lu and coworkers [93] and by the group of Park [94]. In the former study, several guanidines derived from quinidine were synthesized and observed to catalyze the asymmetric amination reaction of α-fluorinated β-ketoesters (Scheme 6.44).



34

Scheme 6.44

Park and coworkers [94] prepared a few derivatives of dihydroquinine with a 2-aminobenzimidazole at C9 (Scheme 6.45) and examined their catalytic potential in the reaction of malonates with nitroalkenes. The derivative with two CF_3 groups in the benzimidazole moiety (**34**) gave, under neutral conditions, rise to



35

Scheme 6.45

higher ee values than species with an unsubstituted benzimidazole. With trifluoroacetic acid as a co-catalyst, the reverse reactivity order was observed and the catalyst with no CF_3 groups in the benzimidazole group gave high yields and enantioselectivity [95].

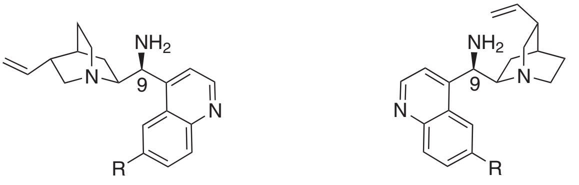
6.6
Cinchona Alkaloids with a Primary Amine Group at C9

6.6.1
Structural Properties

Primary amines derived from cinchona alkaloids have been recognized as excellent catalysts for several asymmetric reactions of, for example, carbonyl compounds. Several reviews have appeared recently on aminocatalysis with derivatives of cinchona alkaloids with a primary amine group at the C9 position [3i, 96]. The amine is installed in a single step by a Mitsunobu reaction of the C9 –OH group in one of the natural cinchona alkaloids (Figure 6.1) [97], thus leading to pseudo-enantiomeric 9-amino-9-deoxy-epi-derivatives of quinine **36** and quinidine **38** (Figure 6.13). The availability of the pseudo-enantiomers allows ready access to both stereoisomers of a chiral product of a given reaction.

The C9 amino derivatives are, of course, diamines, with the primary amino group being important for the covalent activation of carbonyl compounds. The tertiary amino functionality in the quinuclidine ring contributes to the catalytic process as a base forming an ammonium ion or by directing the orientation of the electrophile through hydrogen bonding. In addition, the methoxy group at the C6′ position is converted into a -OH group to improve the hydrogen bonding ability of the C9 amino cinchona catalysts; that is, the C9-amino cupreine **37** and cupreidine **39** are also used for aminocatalysis.

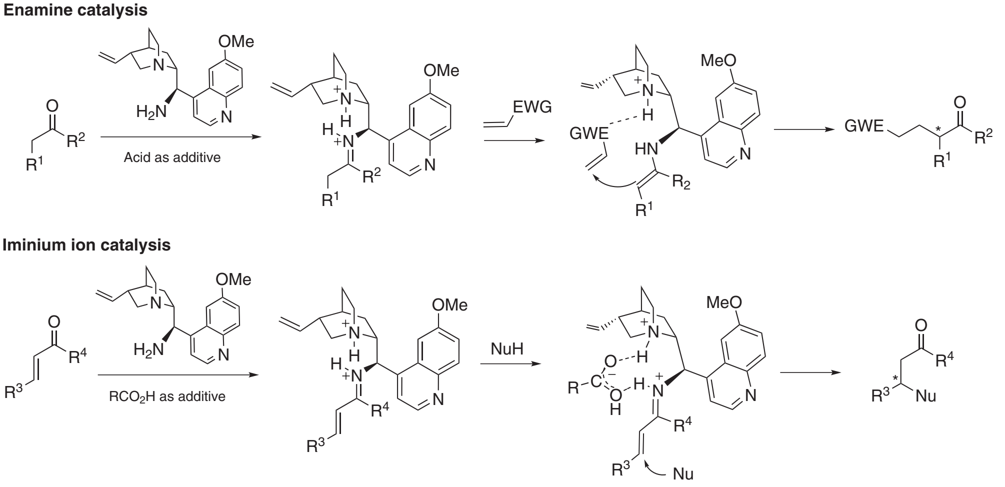
In terms of substrate choice, C9 amino derivatives of the cinchona alkaloids have proven to be suitable for sterically hindered α-branched aldehydes, α-branched unsaturated aldehydes, as well as simple unsaturated ketones and α-branched enones. In general terms, catalysis with the C9 amino derivatives can involve



36 R = OMe
37 R = OH

38 R = OMe
39 R = OH

Figure 6.13 Pseudo-enantiomers 9-amino-9-deoxy-epi-derivatives of quinine **36** and quinidine **38.**


Enamine catalysis

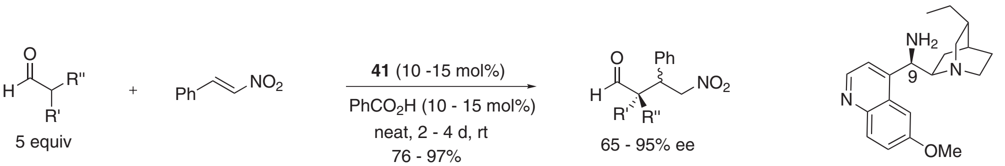
Iminium ion catalysis

Figure 6.14 Simplified scheme for enamine and iminium ion catalysis with C9 amino cinchona alkaloid derivatives.

enamine or iminium ion activation as discussed for various types of organocatalysts with an amine function, for example, proline and derivatives thereof [98]. As illustrated in Figure 6.14 for the C9 amino cinchona derivatives aminocatalysis through enamine of iminium ion activation involves addition of an acid that acts as a co-catalyst.

6.6.2
Catalysis with C9 Amino Derivatives

Different groups reported in 2007 on the use of C9 amino cinchona alkaloids as catalysts for the stereoselective functionalization of branched carbonyl compounds. Connon and coworkers demonstrated that the C9 amino derivative of epidihydroquinine (**40**) and epidihydroquinidine (**41**) were effective catalysts for the conjugate addition of aldehydes and (cyclic) ketones to nitroalkenes via enamine catalysis [99] (Scheme 6.46). The catalysts with the same configuration at C9 as in the natural cinchona alkaloid gave poor results, in line with the results obtained for

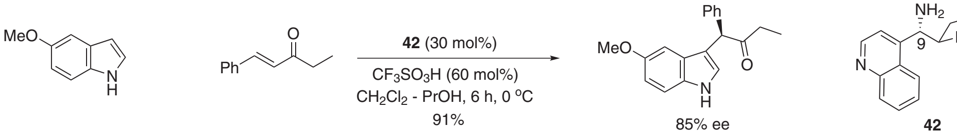


41

Scheme 6.46

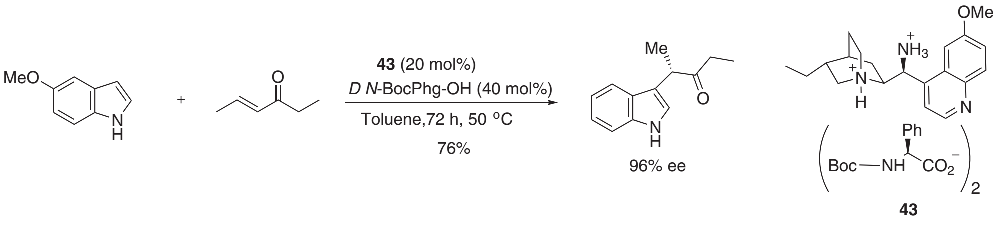
the C9 thiourea derivatives (Section 6.6.2). With **41**, aldehydes and ketones gave the products in high yields and with a pronounced preference for the *syn* diastereomer, even for α-branched aldehydes, though in opposite absolute configuration.

Iminium ion catalysis was demonstrated by Deng and coworkers for the conjugate addition of α,α-dicyanoalkenes to benzylideneacetone with the use of a TFA salt of **36** [100] and by Chen and coworkers for the Friedel–Crafts reaction of indoles with α,β-unsaturated ketones [101] as catalyzed by the C9 amino derivative of cinchonine **42** (Scheme 6.47).



Scheme 6.47

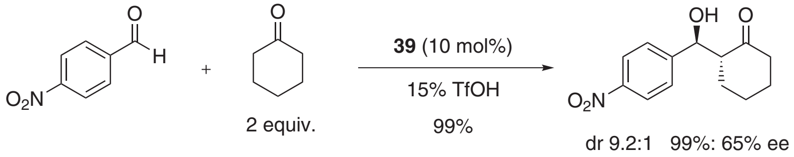
Melchiorre and coworkers have demonstrated independently from the Chen group that salts of C9 amino derivatives of cinchona alkaloids are excellent catalysts for the Friedel–Crafts alkylation of indoles [102]. The salt formed by C9 amino-9-deoxy-epi-dihydroquinine and the D-form of *N*-Boc-phenylglycine **43** (Scheme 6.48) proved to be an excellent catalytic system for the alkylation of indoles via an iminium ion mechanism. The catalytic system **43** was applied successfully for the asymmetric conjugate addition of thiols to α,β-unsaturated ketones [103]. In a study by Song and coworkers, C9 amino-9-deoxy-epicupreine in combination with *N*-Boc-phenylglycine was used as an organocatalytic salt for the enantioselective vinylogous α-ketol rearrangement leading to spirocyclic diketones [104].



Scheme 6.48

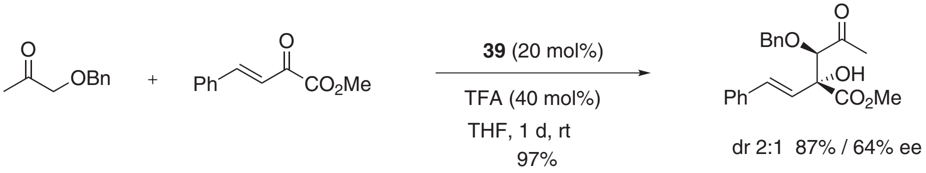
The C9 amino cinchona alkaloid derivatives have been applied in diverse organic reactions, including aldol reactions [105, 106], Knoevenagel condensations [107], and cascade reactions [108]. The first example of an aldol reaction catalyzed by a

C9 amino derivative was reported by Liu and coworkers [105]. The derivative **39** was found to effectively catalyze the enantioselective direct aldol reaction of aldehydes and cyclic ketones, giving the products in high yields, good diastereoselectivity, and high ee's for the major diastereomer (Scheme 6.49).



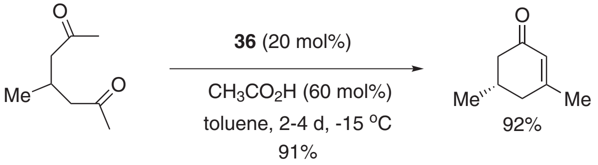
Scheme 6.49

Recently, the asymmetric aldol reaction between the benzyl ether of hydroxyacetone and β,γ-unsaturated-β-ketoesters was reported to be effectively catalyzed by **39** in the presence of TFA, providing the products in high yields, low to moderate diastereoselectivity, and high ee for major diastereomer (Scheme 6.50) [106].



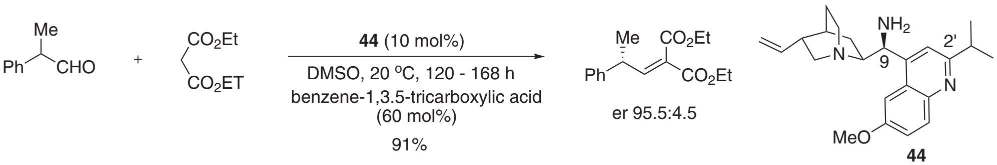
Scheme 6.50

The derivative **39** has also been reported to catalyze the aldol reaction between underivatized hydroxyacetone and activated benzaldehydes, affording the products with low diastereoselectivity and in moderate to high ee [109]. The best results were obtained with (*R,R*)-tartaric acid as co-catalyst and the absence of a solvent. In addition, a scalable procedure for the reaction with 4-nitrobenzaldehyde was developed involving a single crystallization step in order to obtain the enantiopure branched product of the aldol reaction. An example of an intramolecular aldol reaction is provided by work of List and coworkers, who found that the formation of enantioenriched 5-substituted-3-methyl-2-cyclohexene-1-ones could be obtained from 4-substituted-2,6-hexadiones with **36** as the catalyst (Scheme 6.51) [110].



Scheme 6.51

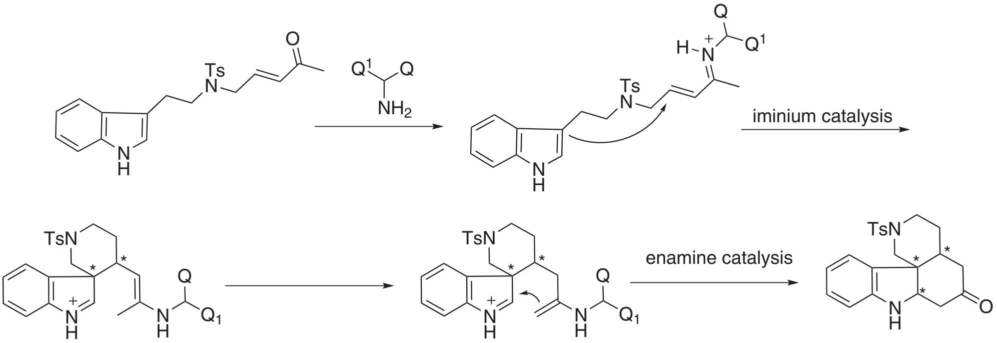
An asymmetric Knoevenagel condensation catalyzed by cinchona alkaloid derivatives has been reported recently by List and coworkers [107]. They examined a series of C9 amino-9-deoxy-epiquinines with an additional aryl or alkyl group at the C2′ position of the quinoline ring (Scheme 6.52). The derivatives all gave rise to good or high yields as well as high enantioselectivities, with the catalyst with an isopropyl group at the C2′ performing slightly better than the rest.



44

Scheme 6.52 Catalysts with a Bu^n, Bu^s, Bu^t, Ph, Bn, and 1-naphthenyl group at C2′ were also studied.

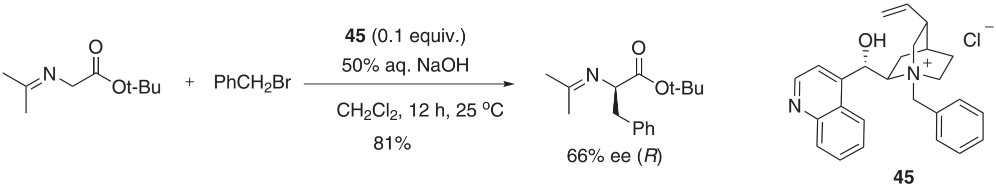
In terms of enamine and iminium ion catalysis, an intramolecular cascade conjugate addition/Mannich reaction was shown to be effectively catalyzed by **36** [108]. The reaction involves the construction of a tetracyclic structure from the indoyl methyl enone shown in Scheme 6.53. The highest enantioselectivities were obtained with addition of nitrobenzoic acid and with ethyl acetate as the solvent.



Scheme 6.53 Cascade reaction with **36** ($QQ^1CH–NH_2$); conditions: catalyst (20 mol%), nitrobenzoic acid (40 mol%), EtOH, 12 h, yield 73% of isolated major diastereomer, dr 86 : 14 and 98% ee (major diastereomer).

6.7
Cinchona Alkaloids in Phase-Transfer Catalysis

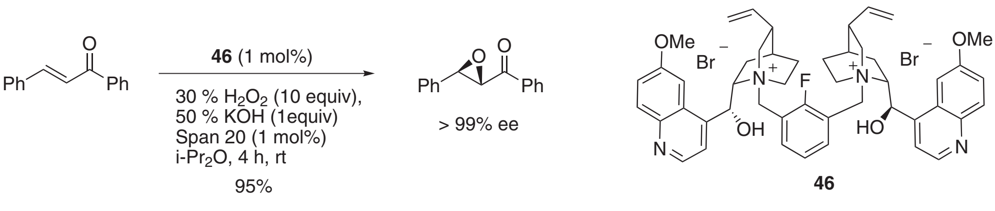
Phase-transfer catalysis is a widely applied method for all kinds of chemical reactions under mild conditions involving ionic intermediates. It is also a recognized strategy for asymmetric transformations even though the relationship between catalyst structure and activity is not fully understood [111]. Indeed, phase-transfer catalysis has in many instances been applied successfully with quaternary ammonium salts derived from natural cinchona alkaloids [112]. The first example of phase-transfer catalysis with a cinchona alkaloid derivative was reported in 1984 by Dolling and coworkers, who employed *N*-*p*-trifluoromethylbenzylcinchonium bromide as catalyst for the enantioselective methylation of an indanone [113]. In 1989, O'Donnell and coworkers demonstrated that selective alkylation of glycine imines could be achieved by phase-transfer catalysis with benzylcinchoninium salt **45** (Scheme 6.54) [114].



Scheme 6.54

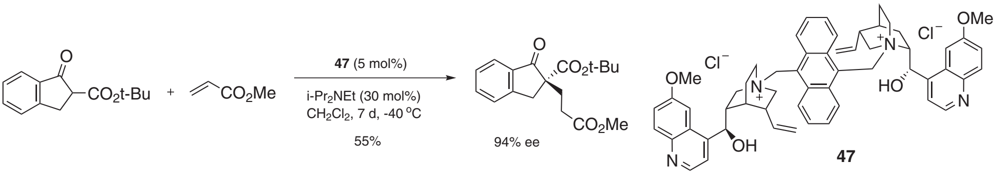
Further development of the cinchona derived catalyst for asymmetric alkylation of glycine imines was obtained by substituting the benzyl group for a 9-methylanthracyl [115] and – in addition – by transformation of the C9 hydroxy group into an allylic or benzylic ether [116]. The catalyst with 9-methylanthracyl group and an allylic ether function gave a good yield and a high enantioselectivity in the alkylation of glycine imines (with PhCH$_2$Br: yield 84%, 94% ee in aq. CsOH, CH$_2$Cl$_2$, at –78 °C, after 23 h).

Phase-transfer catalysis with cinchona alkaloid derivatives is a very active area within the field of organocatalysis, as indicated in quite recent reviews [98c, 112]. In terms of structure, the quaternary ammonium salts can be varied in a straightforward manner by changing the structure of the benzylic compound used for the alkylation of the nitrogen atom of the quinuclidine moiety. In addition, dimeric and trimeric quaternary ammonium salts of cinchona alkaloids have been prepared [112] and applied successfully in catalysis, as exemplified in Scheme 6.55 for the epoxidation of 2,4-diarylenones [117].



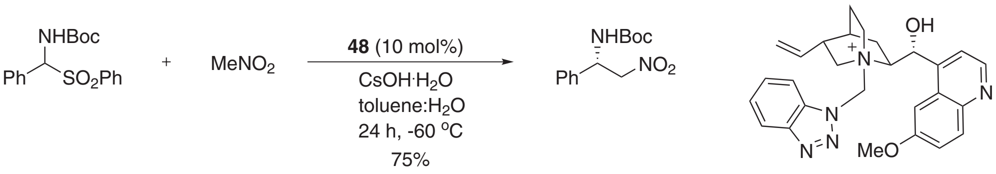
Scheme 6.55

The versatile nature of cinchona alkaloid ammonium salts for phase-transfer catalysis can be illustrated by recent reports on conjugate additions [118] and a nitro-Mannich reaction [119]. Dimeric catalysts derived from quinine and quinidine were applied in the conjugate addition of cyclic β-ketoesters to α,β-unsaturated carbonyl compounds. The reaction proceeded in the presence of a tertiary amine as base and afforded the products in moderate to high yield and enantioselectivity (Scheme 6.56).



Scheme 6.56

N-Benzotriazole derivatives of quinine and quinidine were applied as phase-transfer catalysts for the nitro-Mannich reaction between α-amido-sulfones and nitroalkanes (Scheme 6.57) [119]. The products were formed in good yields and high enantioselectivities and could be transformed efficiently into either a diamine or an α-amino acid.



48

Scheme 6.57

6.8
Ether Bridged Dimers

The C9 ether bridged bis-cinchona derivatives shown in Figure 6.4 are employed in the Sharpless asymmetric hydroxylation [11]. The ready availability of the bis-cinchona derivatives has facilitated their use in organocatalysis, as evidenced by a large number of studies (see, for example, References [3h,i] and [98c]). The most common bis-derivatives contain heteroaromatics with nitrogen atoms or quinone functionalities connecting units between (dihydro) natural cinchona alkaloids (Figure 6.15). Catalysts with a modification in the cinchona moieties are less frequently applied. In a recent study, a bis-cinchona derivative with a hydroxyl group

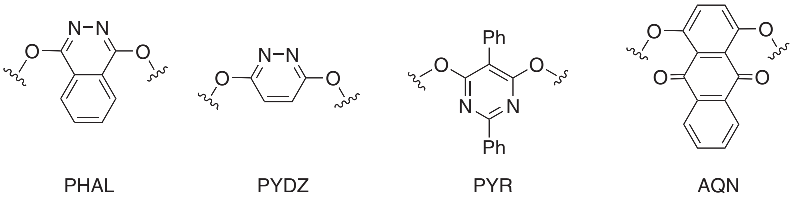
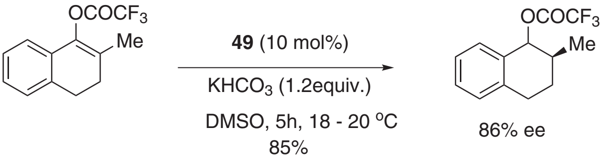


Figure 6.15 Common aromatic groups connecting dihydroquinine (DHQ) or dihydroquinidine (DHQD) in bis-cinchona alkaloid derivatives.

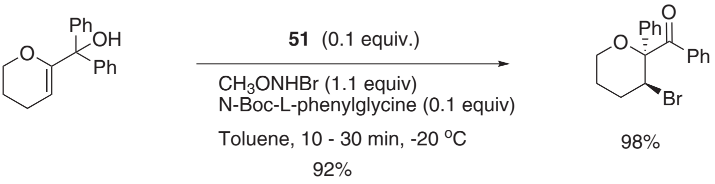
at the C6′ position was prepared and observed to be an effective catalyst for the conjugate addition of malonates to β-nitroalkenes [120]. Bis-cinchona derivatives have also been modified for phase-transfer catalysis by converting one of the cinchona units into a quaternary ammonium salt [121].

The bis-cinchona alkaloids have been shown to be efficient and enantioselective catalysts for a wide range of asymmetric reactions. A $(DHQ)_2AQN$ (AQN: 9,10-anthraquinone-1,4-diyl) compound (**49**) is reported to catalyze the protonation of enol trifluoroacetates in the presence of hydrogen carbonate and with formation of the products in good yield and enantioselectivity (Scheme 6.58) [122].



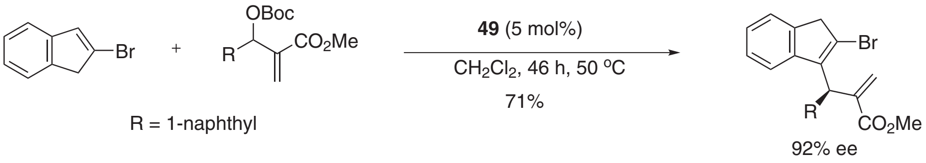
Scheme 6.58

Halogenation reactions were also shown to be catalyzed by bis-cinchona alkaloids, for example, $(DHQ)_2PHAL$ (PHAL: 1,4-phthalazinediyl) (**50**) was reported to catalyze the fluorocyclization of indoles [123] and $(DHQD)_2PYR$ (PYR: 2,5-diphenyl-4,6-pyrimidinediyl) (**51**) [124] as well as $(DHQD)_2PYDZ$ (PYDZ: 3,6-pyridazinediyl) (**52**) [125] were shown to catalyze halogenation/semipinacol rearrangements (Scheme 6.59).


Ph
OH
O
Ph
51 (0.1 equiv.)
CH3ONHBr (1.1 equiv)
N-Boc-L-phenylglycine (0.1 equiv)
Toluene, 10 - 30 min, -20 °C
92%
O
Ph
O
Ph
Br
98%

Scheme 6.59

Bis-cinchona derivatives with a PHAL or AQN moiety have recently been applied for organocatalytic reactions with Morita–Baylis–Hillman carbonates [126], as shown in Scheme 6.60 for an asymmetric allylic alkylation of indenes [126c].

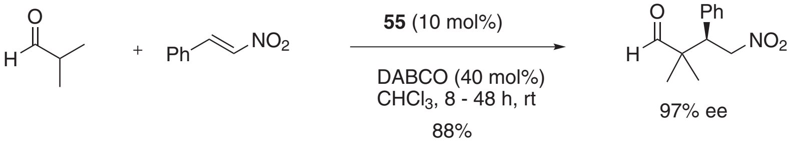


Scheme 6.60

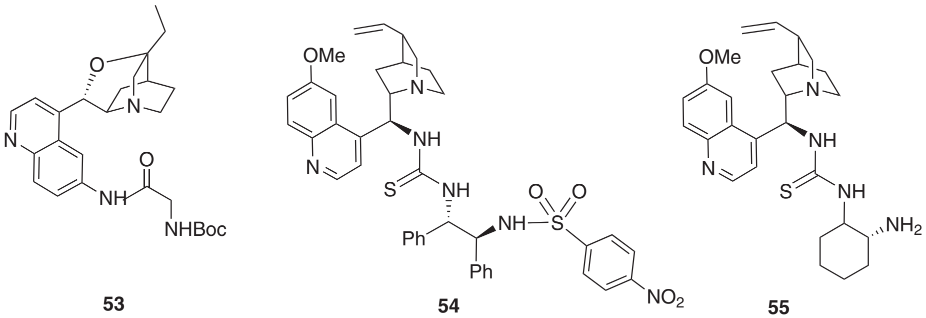
6.9
Some Novel Cinchona Alkaloid Derivatives

New cinchona derivatives are continuously being developed for application in asymmetric organocatalysis. Examples of catalysts obtained by further modification of existing derivatives include an *N*-oxide of dihydrocupreidine [127], a C6′-*N*-Boc-glycine-β-isocupreine (**53**) [128], a C9 thiourea substituted at a remote site with a sulfonamide group (**54**) [129, 130], and catalysts with an amine as well as a thiourea group (**55**) [131] (Figure 6.16).

The cinchona alkaloid derivative **55** was found to be an outstanding catalyst for the conjugate addition of aldehydes to nitroalkenes (Scheme 6.61).



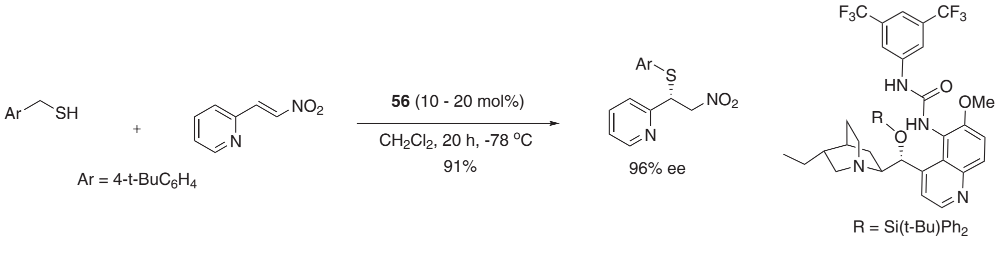
Scheme 6.61



53 **54** **55**

Figure 6.16 Examples of catalysts obtained by further modification of existing derivatives.

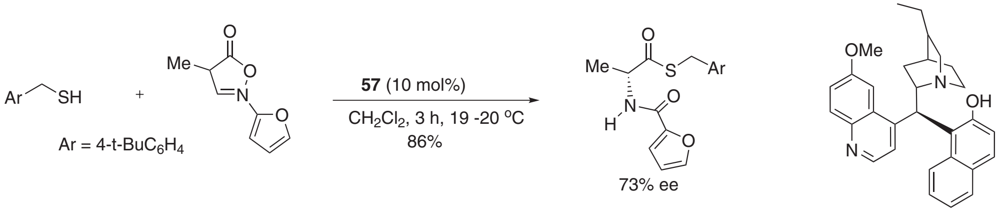
Cinchona alkaloids with a urea at the C5′ position were prepared recently and found to be efficient enantioselective catalysts for nitroaldol reactions [132] and conjugate additions of thiols to nitrostyrenes (Scheme 6.62) [133].



56

Scheme 6.62

An entirely different class of derivatives was prepared by Skarżewski and his group [134] who introduced a phenyl, a 4-hydroxyphenyl, or a 1-naphthyl group at C9 by first substituting the C9 hydroxy group for a halogen atom prior to reaction with a Grignard reagent. Recently, Connon and coworkers prepared a series of C9 cinchona alkaloids modified with a naphthol group and obtained low to good yields and moderate to high enantioselectivity in the dynamic kinetic resolution of azalactones with prop-2-ene-1-ol [135] or thiols [136] (Scheme 6.63).



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Scheme 6.63

6.10
Prospects

This gives chapter an overview of natural cinchona alkaloids and synthetic derivatives together with examples of their use in asymmetric organocatalysis. In recent years, the emphasis has been on the development of cinchona-based bifunctional catalysts, in particular species with a thiourea moiety. The search for new cinchona-based organocatalysts continues and new derivatives are relentlessly being prepared and applied for specific enantioselective reactions. The design of these new derivatives is still based mainly on an empirical strategy and to a lesser extent on an understanding of the mechanism of the organocatalytic reactions. Even though the experimental approach to the design of new derivatives is likely to be fruitful also in the coming years a more fundamental understanding of organocatalysis is likely to be vital for efficient development of improved and generally applicable catalysts based on the privileged cinchona alkaloid structure.

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7

Chiral C_2 Catalysts

Daisuke Uraguchi, Kohsuke Ohmatsu, and Takashi Ooi

7.1

Introduction

As clearly seen from the list of so-called privileged chiral ligands and catalysts [1], having a C_2-symmetry in their structures is quite important and advantageous for being able to control stereochemical outcome of a broad range of chemical transformations because it reduces the number of possible competing, diastereomeric transition states. In this regard, axially chiral molecular frameworks, most commonly biaryls, are particularly attractive to be adopted as a structural backbone and have been strategically utilized for the design of C_2-symmetric ligands and catalysts. This chapter focuses on outlining the features of organocatalysts that have been developed on the basis of this conceptual background. The structures and catalytic performance of representative catalysts in this category, including some mechanistic aspects, are described according to their functions depending on the prime functional groups they possess.

7.2

Chiral Lewis Base Catalysts

Asymmetric catalysis based on the catalytic activation of otherwise less-reactive nucleophiles by coordination with a chiral, non-racemic Lewis base is a powerful strategy for promoting nucleophilic addition to carbonyl compounds and other synthetically useful electrophiles in a highly stereocontrolled manner. The development and applications of chiral C_2-symmetric organic molecules possessing appropriate Lewis basic/nucleophilic functionalities have made significant contributions to the advancement of this field of research during the past two decades. Representative structures of this type of catalyst manifold and the performance of each catalyst class in a typical stereoselective bond-forming reaction are delineated in this section.

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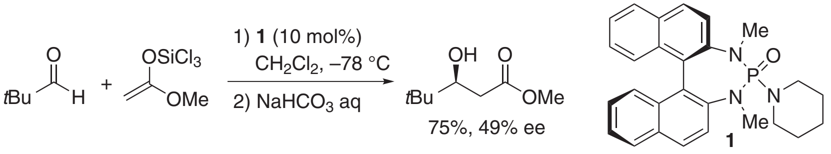
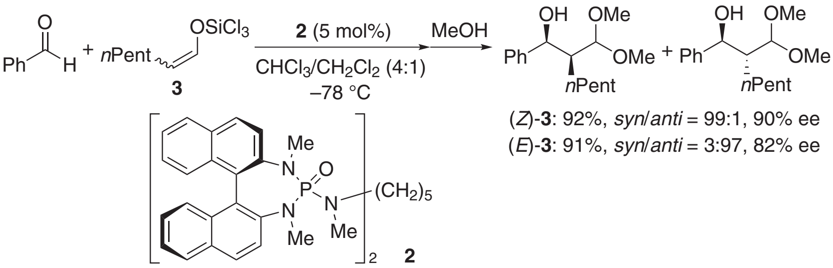
7.2.1
Phosphoramides

In 1996, Denmark introduced chiral phosphoramide **1**, which could be readily synthesized from the parent commercially available (*R*)-2,2′-diamino-1,1′-binaphthalene, as an effective catalyst for the aldol reaction of the preformed trichlorosilyl enol ether of methyl acetate with aldehydes under mild conditions (Scheme 7.1) [2].



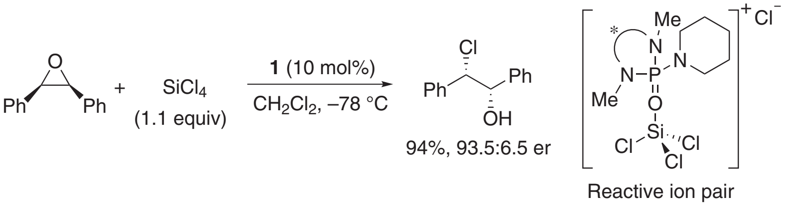
Scheme 7.1 Chiral phosphoramide-catalyzed aldol reaction.

This system could be successfully extended to the catalytic enantioselective crossed-aldol reaction of aldehydes [3]. The geometrically defined (*E*)- and (*Z*)-trichlorosilyl enol ethers of aldehydes underwent efficient, highly diastereoselective addition to different aldehydes under the influence of chiral bis-phosphoramide **2**, which possess a tether of five methylene units, to give the corresponding *anti*- and *syn*-β-hydroxy aldehydes as a form of dimethyl acetal, respectively, with good yet variable enantioselectivity (Scheme 7.2).



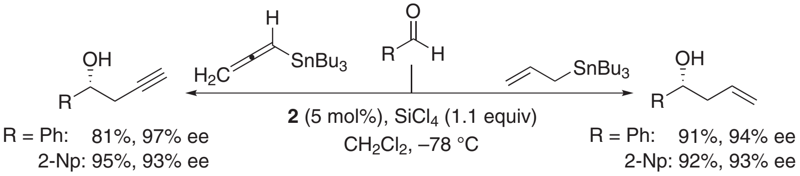
Scheme 7.2 Stereoselective crossed-aldol reaction of aldehydes.

In addition, this class of chiral phosphoramides could catalyze the enantioselective ring opening of epoxides with silicon tetrachloride ($SiCl_4$) [4]. For instance, the reaction of *cis*-stilbene oxide with $SiCl_4$ proceeded smoothly in the presence of **1** to afford the desired chlorohydrin in an enantiomerically enriched form (Scheme 7.3). The reactive ion pair shown in the scheme was proposed to be generated through the activation of $SiCl_4$ by the coordination of one phosphoramide **1**, serving to activate the epoxide; it was confirmed that bis-phosphoramide **2** was far less selective in this reaction.



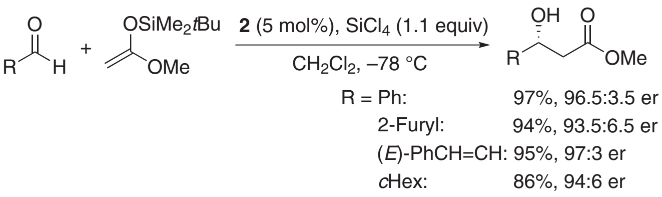
Scheme 7.3 Ring opening of *meso*-epoxides in combination with $SiCl_4$.

Denmark has also made significant contributions to the evolution of this chemistry by introducing the concept of Lewis base activation of Lewis acids. Its validity and synthetic potential were demonstrated first by achieving the highly enantioselective allylation and propargylation of aldehydes with **2** as an optimal catalyst as exemplified in Scheme 7.4 [5]. The key to this asymmetric catalysis is the generation of a chirally modified and activated silicon Lewis acid by the **2**-promoted ionization of the weakly Lewis acidic $SiCl_4$.



Scheme 7.4 Catalytic activation of $SiCl_4$ with chiral bis-phosphoramide **2.**

This concept has been further applied to the development of various stereoselective bond-forming reactions using chiral bis-phosphoramides as catalysts. The most well-explored system is the aldol addition of silyl ketene acetals to aldehydes [6]. In general, combination of a catalytic amount of **2** and a stoichiometric quantity of $SiCl_4$ was very effective for the reactions of methyl acetate-derived silyl ketene acetal with various aldehydes (Scheme 7.5).



Scheme 7.5 Aldol reaction of silyl ketene acetal.

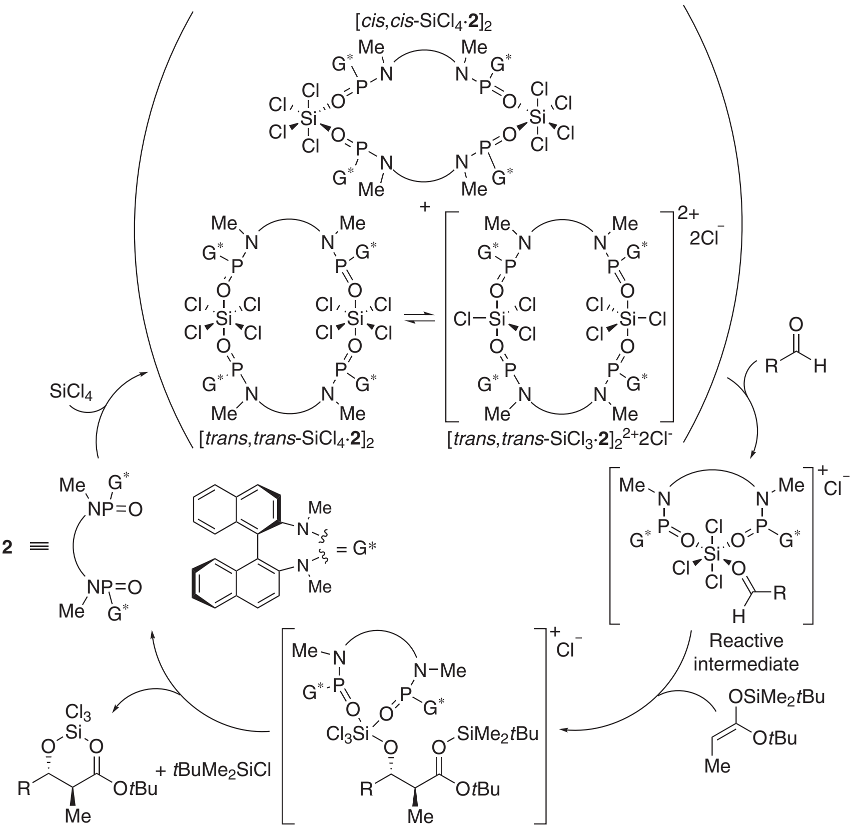
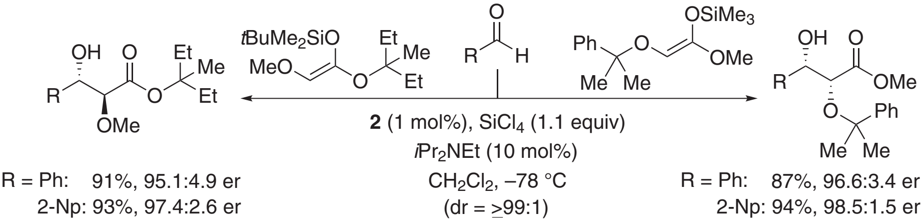


Figure 7.1 Plausible catalytic cycle.

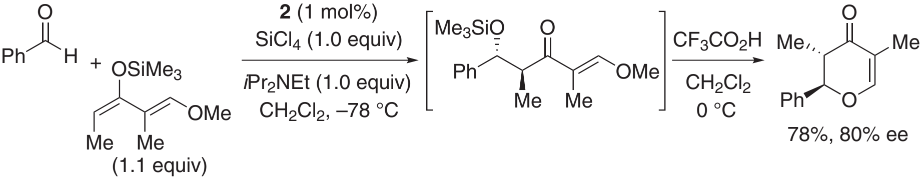
The in-depth mechanistic studies on this catalytic asymmetric aldol reaction showed that the most enantioselective catalyst (**2**), upon interacting with SiCl$_4$, generated a ternary mixture of neutral and cationic dimers [*cis,cis*-SiCl$_4\cdot$**2**]$_2$, [*trans,trans*-SiCl$_4\cdot$**2**]$_2$, and [*trans,trans*-SiCl$_3\cdot$**2**]$_2^{2+}$2Cl$^-$ (Figure 7.1). From the ground state to the transition state, the dimers dissociated to form the reactive intermediate, and the cationic, five-coordinated complex [*trans,trans*-SiCl$_3\cdot$**2**]$_2^{2+}$2Cl$^-$ would probably be the immediate precursor of the reactive intermediate. After carbon–carbon bond formation with silyl ketene acetal, **2** was regenerated through derivatization of the trichlorosilyl alkoxide [7].

The synthetic utility of this process was enhanced by the development of the glycolate aldol reaction as illustrated in Scheme 7.6. An important feature was that both *syn*- and *anti*-1,2-diols could be obtained under identical conditions by appropriately modulating the steric size of the substituents on the silyl ketene acetals [8].



Scheme 7.6 Glycolate aldol reaction.

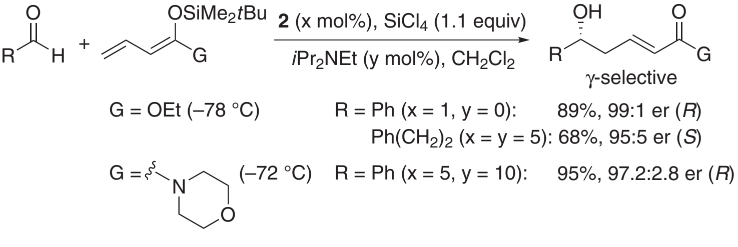
Another intriguing application reported by Scettri was the *trans*- and enantioselective synthesis of 2,3-disubstituted 2,3-dihydropyran-4-ones through the **2**-catalyzed aldol reaction of the siloxy diene with aldehydes followed by acidic treatment for the subsequent ring closure (Scheme 7.7) [9].



Scheme 7.7 Hetero-Diels–Alder reaction.

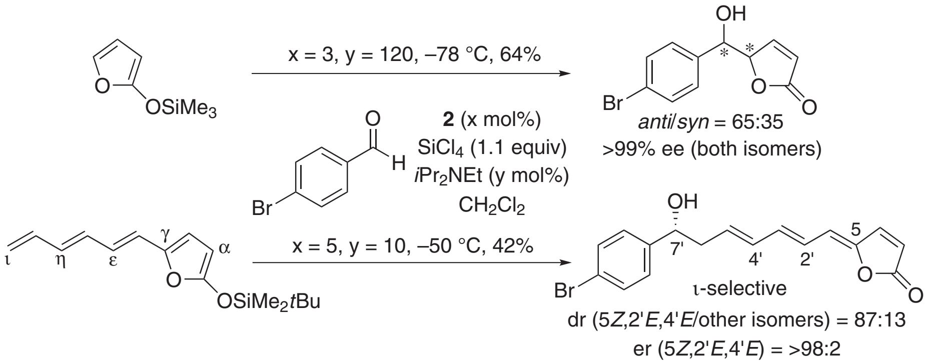
This system could be evolved into the catalytic enantioselective vinylogous aldol reactions [10, 11]. For example, the reaction of crotonate-derived dienol ether with benzaldehyde proceeded smoothly in the presence of **2** to give the γ-addition product exclusively with rigorous enantiocontrol (Scheme 7.8). This protocol tolerated the use of aliphatic aldehydes such as 3-phenylpropanal as an electrophile and has found fruitful applications in the total synthesis of natural products [12].

With respect to variation of the nucleophile component in the vinylogous aldol methodology, α,β-unsaturated amide-derived, conjugated *N,O*-silyl ketene acetals could be employed under similar conditions as included in Scheme 7.8 [13].


R
H
O
+
OSiMe2tBu
G
2 (x mol%), SiCl4 (1.1 equiv)
iPr2NEt (y mol%), CH2Cl2
OH
O
R
G
γ-selective
G = OEt (–78 °C)
R = Ph (x = 1, y = 0): 89%, 99:1 er (R)
Ph(CH2)2 (x = y = 5): 68%, 95:5 er (S)
G =
N
O
(–72 °C)
R = Ph (x = 5, y = 10): 95%, 97.2:2.8 er (R)

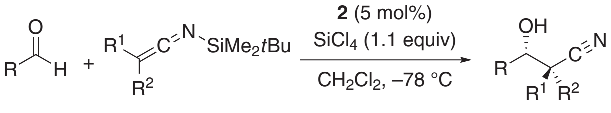
Scheme 7.8 Vinylogous aldol reactions.

Moreover, Palombi showed that 2-trimethylsiloxyfuran was a good candidate, making it feasible to access δ-hydroxy butenolides stereoselectively (Scheme 7.9) [14]. To further expand the scope, Curti demonstrated that *N*-Boc 2-siloxypyrrole was amenable [15] and also developed **2**-catalyzed hyper-vinylogous reactions using extended furan-based siloxy polyenes [16].



Scheme 7.9 Scope of vinylogous donors.

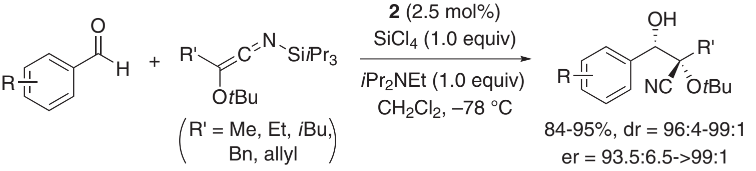
As an elaborated silyl nucleophile, silyl ketene imines were an attractive candidate for participation in the $SiCl_4$-promoted, chiral Lewis base-catalyzed stereoselective addition to aldehydes. For example, the reaction of silyl ketene imine, prepared by lithiation of α-phenylpropionitrile followed by trapping with tBuMe$_2$SiCl, with benzaldehyde under typical conditions with bis-phosphoramide **2** as a catalyst afforded the nitrile product in good yield with high levels of diastereo- and enantioselectivity (Scheme 7.10) [17]. This method was applicable to various aromatic aldehydes and also general in the structure of silyl ketene imine, offering a powerful strategy for the construction of quaternary stereocenters bearing nitrile functionality.



R	R^1	R^2	yield	dr	er
Ph	Ph	Me	87%	95:5	98.5:1.5
Ph	4-MeOC$_6$H$_4$	Me	90%	99:1	99.1:0.9
2-Np	Ph	*i*Bu	90%	99:1	99.6:0.4
2-Furyl	Ph	Me	92%	99:1	94.9:5.1

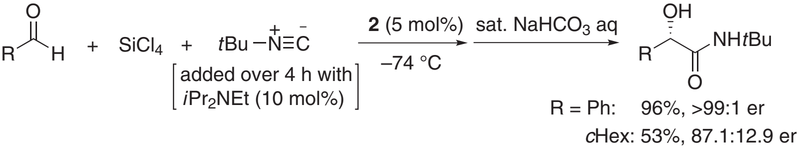
Scheme 7.10 Aldol addition of silyl ketene imines to aldehydes.

Furthermore, *N*-silyl oxyketene imines derived from protected cyanohydrins were found to serve as acyl anion equivalents in a similar reaction manifold, enabling the efficient preparation of cross-benzoin and glycolate-aldol products in an almost stereochemically pure form (Scheme 7.11) [18].



Scheme 7.11 Addition of *N*-silyl oxyketene imines catalyzed by **2.**

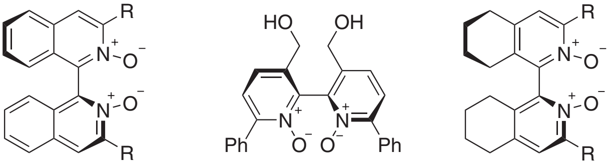
An advantage of this type of asymmetric catalysis was also featured by application to the development of an enantioselective α-addition of isocyanides to aldehydes (Scheme 7.12) [19], which was difficult to achieve with chiral Lewis acid catalysts due to problems associated with the formal divalency of isocyanide.



Scheme 7.12 Asymmetric α-addition of isocyanide.

7.2.2
Bipyridine *N,N′*-Dioxides

Taking into consideration the fact that amine *N*-oxides exhibit an eminent nucleophilicity toward silicon atom, Nakajima introduced (*S*)-3,3′-dimethyl-2,2′-biquinoline *N,N′*-dioxide (**4**) as an effective catalyst for the enantioselective addition of allyltrichlorosilanes to aldehydes (Scheme 7.13) [20a]. In this system, the use of *N,N*-diisopropylethylamine as an additive proved to be crucial for accelerating the catalytic cycle without affecting the sense and extent of the enantioselection. The role of the amine additive might be to promote dissociation of **4** from the silicon atom in the product through ligand exchange for the regeneration of **4.** A practical extension of this approach was the establishment of a one-pot procedure for the enantioselective synthesis of homoallylic alcohols, which involved the *in situ* generation of allyltrichlorosilanes from allyl halides in the presence of cuprous chloride and tertiary amine followed by the reaction with aldehydes catalyzed by **4** [20b].

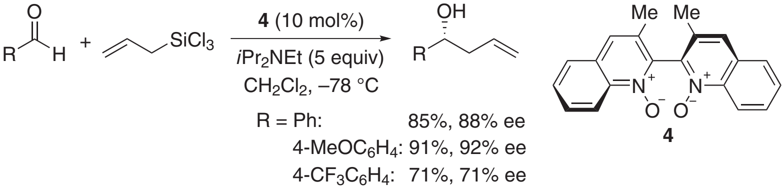


5a (R = H)
b (R = Ph)

6

7a (R = Ph)
b (R = (*R*)-Tetrahydrofuran-2-yl)

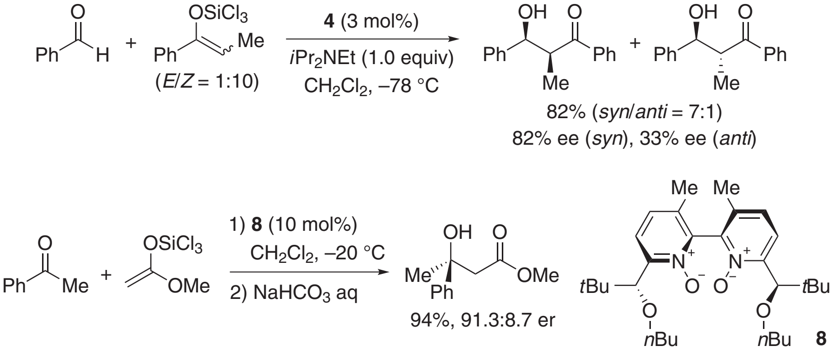
Figure 7.2 Axially chiral *N*,*N*′-dioxides for asymmetric allylation.



Scheme 7.13 Enantioselective allylation of aldehydes.

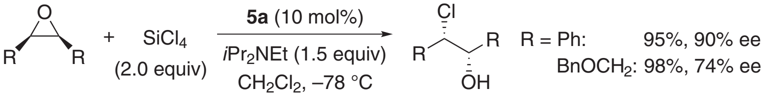
Since this study, several axially chiral C_2-symmetric *N*,*N*′-dioxides of related structures such as **5** [20a, 21], **6** [22], and **7** [23] have been reported (Figure 7.2) and their reactivity and selectivity were evaluated in the asymmetric allylation of aldehydes with allyltrichlorosilane under similar conditions.

This class of chiral Lewis base catalysts was also applicable to the enantioselective aldol reactions of trichlorosilyl enol ethers (Scheme 7.14) [24, 25]. As included in Scheme 7.14, Denmark devised chiral bipyridine *N*,*N*′-dioxide **8** and demonstrated that it smoothly catalyzed the aldol addition of methyl acetate-derived trichlorosilyl ketene acetal to a series of ketones with good to high enantioselectivities [25].



Scheme 7.14 Aldol additions of trichlorosilyl enol ethers.

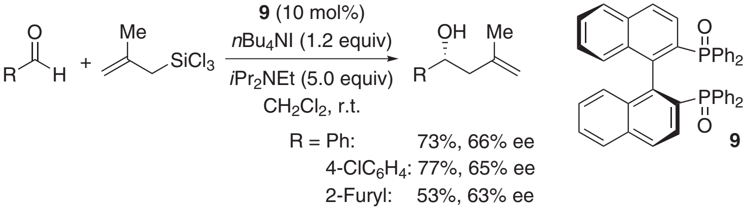
Used in combination with $SiCl_4$, Nakajima elicited the ability of (*S*)-1,1′-biisoquinoline *N,N′*-dioxide (**5a**), which was inferior to **4** in the allylation of aldehydes, as a catalyst for the asymmetric chloride ring opening of *meso*-epoxides via the formation of a hexacoordinated silicate intermediate (Scheme 7.15) [26].



Scheme 7.15 Ring opening of *meso*-epoxides.

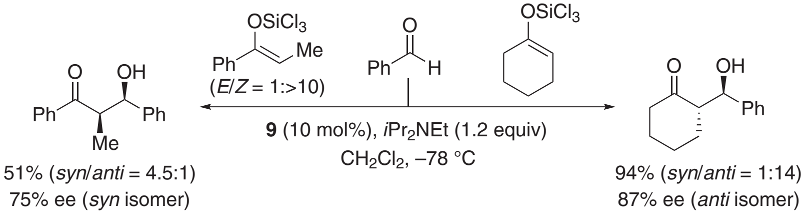
7.2.3
Bisphosphine Dioxides

After Kobayashi's pioneering study on the ability of (*S*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl dioxide (**9**, BINAPO) as a promoter of the enantioselective allylation of α-hydrazono esters with allyltrichlorosilanes [27], Nakajima reported the first catalytic system for the allylation of aldehydes, in which the use of *N,N*-diisopropylethylamine and tetrabutylammonium iodide was essential for accelerating the catalytic cycle (Scheme 7.16) [28]. For this allylation, γ-functionalized nucleophiles such as *cis*-γ-bromoallyltrichlorosilane could be employed as addressed by Malkov and Kočovský [29]. In addition, **9** could be applied to the asymmetric ring opening of *meso*-epoxides with $SiCl_4$, as expected from the scope of the chiral bipyridine *N,N′*-dioxide catalysis [30], and could also catalyze the $SiCl_4$-mediated, enantioselective phosphonylation of aldehydes with trialkyl phosphites [31].

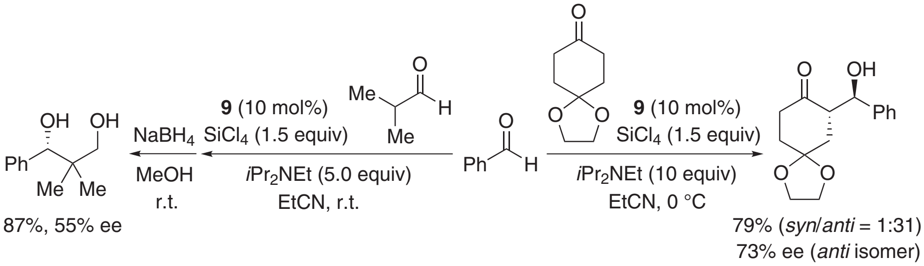


Scheme 7.16 Chiral bisphosphine dioxide-catalyzed enantioselective allylation.

The potential of **9** as a chiral Lewis base catalyst was further demonstrated by application to the aldol reaction of trichlorosilyl enol ethers of ketones with aldehydes, which proceeded with high diastereo- and enantioselectivity [32]. The observed stereospecificity suggested the intervention of a six-membered cyclic transition state (Scheme 7.17). Notably, enolization of cyclohexanone derivatives and aliphatic aldehydes appeared feasible by $SiCl_4$ with the assistance of amine base and **9**, leading to the establishment of a new protocol for direct aldol-type reactions between ketones and aldehydes or two aldehydes (Scheme 7.18) [33].

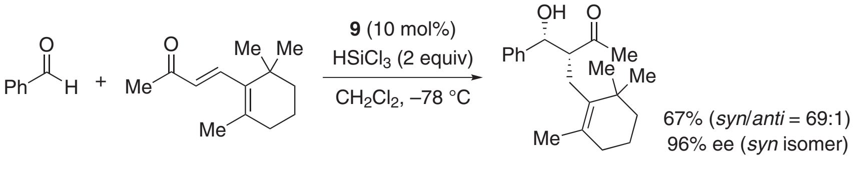


Scheme 7.17 Aldol reactions of trichlorosilyl enol ethers.



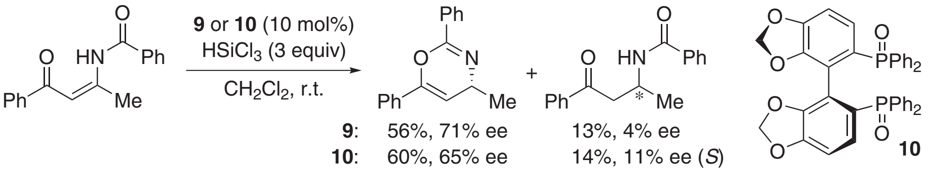
Scheme 7.18 Direct cross aldol reactions.

Nakajima and Sugiura also achieved the **9**-catalyzed, enantioselective conjugate reduction of α,β-unsaturated ketones using trichlorosilane as a hydride source [34]. This method was developed into a one-pot reductive aldol reaction by taking advantage of the insusceptibility of aldehydes toward reduction under these conditions, giving rise to the corresponding β-hydroxy ketone with rigorous diastereo- and enantio-controls (Scheme 7.19). The *syn*-selectivity could be ascribed to *in situ* formation of the (*Z*)-trichlorosilyl enolate followed by **9**-catalyzed aldol reaction through a six-membered chair-like transition state.



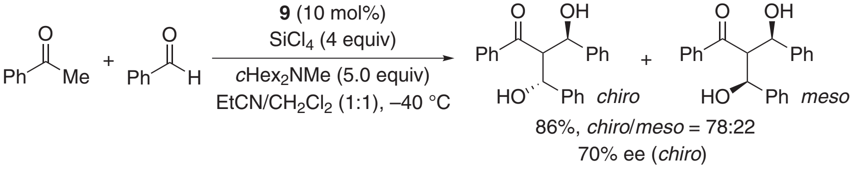
Scheme 7.19 One-pot reductive aldol reaction.

In a related manner, *N*-acylated β-amino enones experienced reductive cyclization under the catalysis of a chiral Lewis base to preferentially furnish enantioenriched 4*H*-1,3-oxazines, where trichlorosilane acted not only as a reductant but also as a dehydrating agent [35]. The selectivity of **9** was revealed to be superior to that of SEGPHOS-derived **10** (Scheme 7.20).



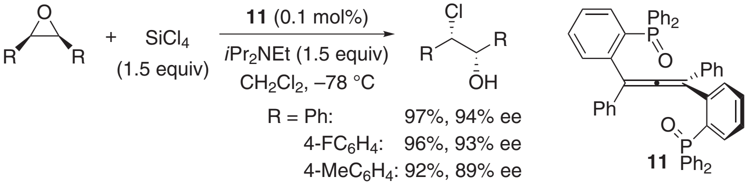
Scheme 7.20 Enantioselective reductive cyclization.

Furthermore, the combined use of a catalytic amount of **9** with $SiCl_4$ allowed for the broadly useful, stereoselective double aldol reaction of ketones with aldehydes as depicted in Scheme 7.21 [36]. This asymmetric transformation involved the initial cross aldol reaction between ketone and aldehyde controlled by **9** and subsequent enolization of the resulting trichlorosilyl ether activated by **9** to generate the chiral cyclic enol ether that, in turn, underwent a second aldol process with another aldehyde in a diastereoselective fashion.



Scheme 7.21 Stereoselective double aldol reaction.

From an essentially different angle, Ready pursued the design of chiral phosphine oxides containing an allene backbone and prepared bisphosphine dioxide **11**, which was found to exert remarkably high catalytic efficiency in the ring opening of *meso*-epoxides in combination with $SiCl_4$, affording the corresponding chlorohydrin in high yields with good to excellent stereocontrol (Scheme 7.22) [37].

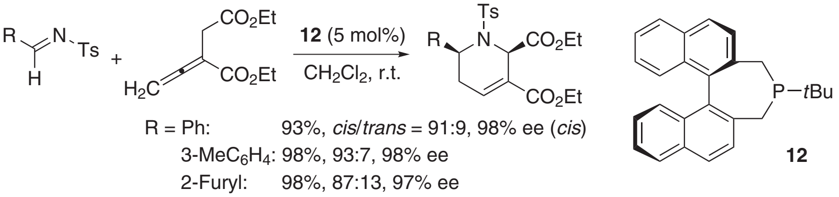


Scheme 7.22 Allene-containing chiral bisphosphine dioxide as catalyst.

7.3
Phosphines

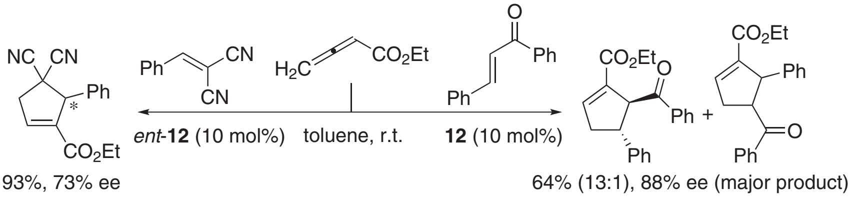
Tertiary phosphines have been recognized as effective catalysts for a range of organic transformations. Accordingly, the development and applications of chiral tertiary phosphines has been a subject of great interest, and axially chiral C_2-symmetric mono- and bis-phosphines have been developed in this context.

On the basis of the Kwon's pioneering study on the tributylphosphine-catalyzed [4+2] annulation of allenes with imines and the possibility of stereocontrol by use of chiral phosphine [38], Fu demonstrated that a binaphthyl-based tertiary phosphine having the bulky *tert*-butyl substituent (**12**) [39] served as a powerful catalyst for this reaction, enabling the facile construction of various synthetically useful piperidine derivatives with excellent levels of relative and absolute stereocontrol (Scheme 7.23) [40].


R
N
Ts
H
+
CO2Et
CO2Et
H2C
12 (5 mol%)
CH2Cl2, r.t.
Ts
R
N
CO2Et
CO2Et
R = Ph: 93%, cis/trans = 91:9, 98% ee (cis)
3-MeC6H4: 98%, 93:7, 98% ee
2-Furyl: 98%, 87:13, 97% ee
P−tBu
12

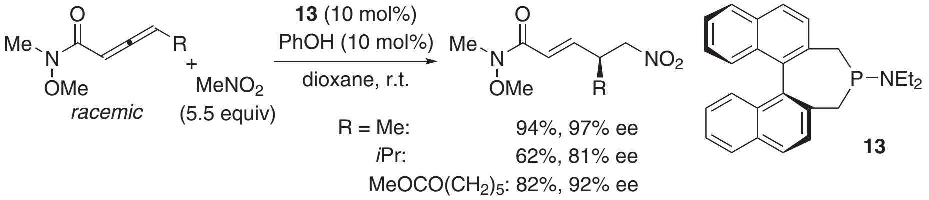
Scheme 7.23 Chiral phosphine **12**-catalyzed [4+2] annulation.

Furthermore, **12** was found to catalyze [3+2] cycloaddition of allenes with various β-substituted α,β-unsaturated ketones to produce enantiomerically enriched, highly functionalized cyclopentenes possessing two contiguous stereocenters [41]. Along with this line, Marinetti reported that 2-aryl-1,1-dicyanoethylenes were also good reaction partners of the allenoates in the **12**-catalyzed cycloaddition [42] (Scheme 7.24).



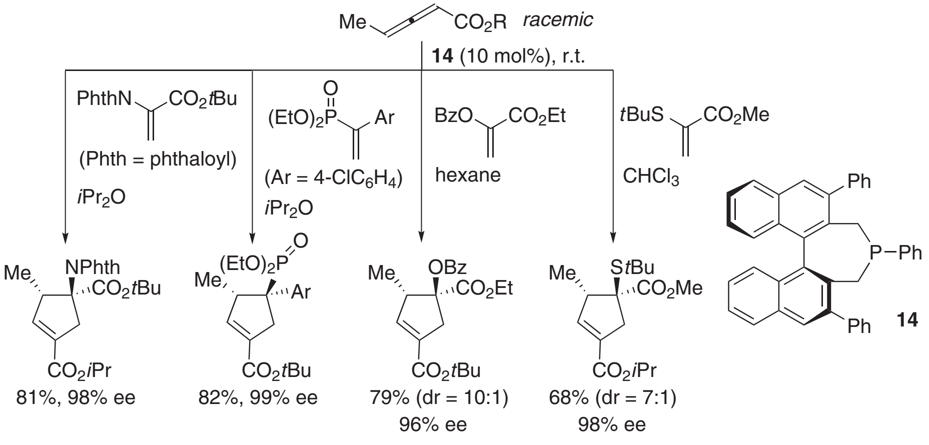
Scheme 7.24 [3+2] cycloadditions.

While the C_2-symmetric aminophosphine **13** was known as a chiral ligand [43], Fu utilized it as a nucleophilic catalyst for development of the γ addition of nitromethane to racemic allenes bearing a Weinreb amide, which proceeded at room temperature with good enantioselectivity (Scheme 7.25) [44]. The product of this transformation is a chiral α,β-unsaturated carbonyl compound that can be further functionalized at the α and β positions in a stereoselective manner.



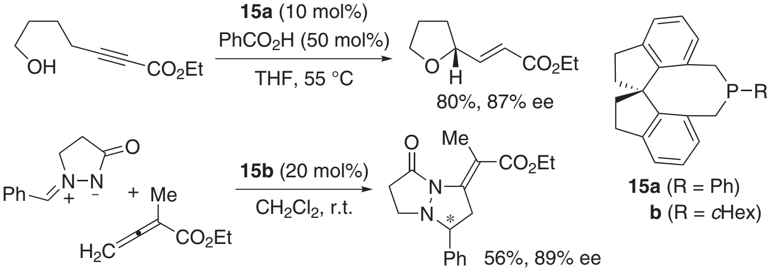
Scheme 7.25 Chiral phosphine-catalyzed addition of nitromethane to allenes.

During continuous research efforts, Fu designed and synthesized new tertiary phosphines of type **14** that made it feasible to develop catalytic diastereo- and enantioselective [3+2] cycloadditions of racemic, γ-substituted allenoates and allenamides with functionalized electron-deficient olefins, thus providing stereoconvergent processes to access structurally and stereochemically diverse cyclopentenes with heteroatom (N, P, O, and S)-substituted quaternary stereocenters (Scheme 7.26) [45].



Scheme 7.26 [3+2] cycloadditions of racemic, γ-substituted allenoates.

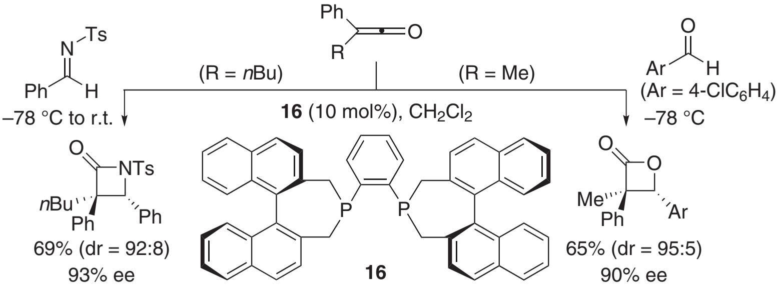
Meanwhile, Fu shed light on the effectiveness of chiral spiro phosphine **15a** [46] as an efficient nucleophilic catalyst for achieving the asymmetric intramolecular cyclization of hydroxyl-2-alkynoates into saturated oxygen-containing heterocycles such as tetrahydrofurans, tetrahydropyrans, and dihydrobenzopyrans (Scheme 7.27) [47]. In addition, Kwon employed this class of phosphine (**15b**) to gauge the



Scheme 7.27 Effectiveness of chiral spiro phosphines.

feasibility of developing enantioselective [3+2] cycloaddition of azomethine imines with allenoates, and indeed the annulation product was obtained in a synthetically useful yield with high enantiomeric excess [48].

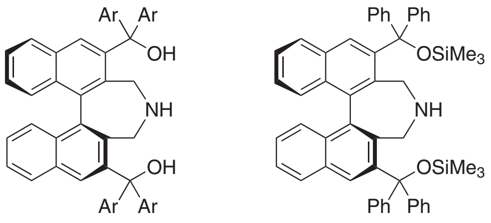
Starting from the initial promising result in an attempt at enantioselective ketene dimerization using chiral bisphosphine **16** [49] as a catalyst [50], Kerrigan clearly demonstrated the potential of the nucleophilic catalysis of **16** in applications to the formal [2+2] cycloaddition of ketoketenes with aldehydes and *N*-tosyl arylimines, which offered access to a wide range of highly substituted β-lactones and β-lactams, respectively, with good to high degrees of diastereo- and enantiocontrol (Scheme 7.28) [51].



Scheme 7.28 Formal [2+2] cycloaddition of ketenes with aldehydes and imines.

7.4
Chiral C_2-Symmetric Secondary and Primary Amines

The design and synthesis of a new class of chiral secondary amines represents a powerful approach to greatly expanding the scope of asymmetric catalysis based on the generation of enamine and iminium ions as a reactive intermediate. Maruoka has made significant contributions to this field of research through the development of a series of binaphthyl-derived, axially chiral C_2-symmetric secondary amines of type **17** and **18** (Figure 7.3).

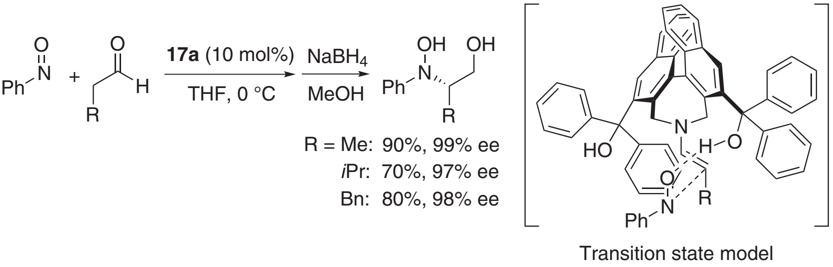


17a (Ar = Ph), **b** (Ar = C_6F_5)

18

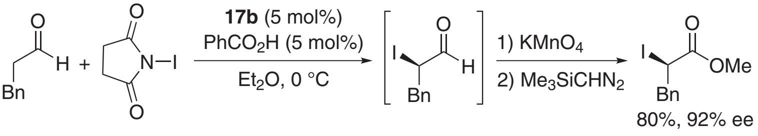
Figure 7.3 Designer chiral secondary amine catalysts.

He initially developed a direct, highly enantioselective hydroxyamination of aldehydes with nitrosobenzene based on the use of **17a** having two diphenylhydroxymethyl groups as a requisite catalyst [52]. In the possible transition state model for this reaction, the *Re* face of the enamine was effectively shielded by one diphenylhydroxymethyl group and another hydroxy functionality participated in directing and activating the nitrosobenzene via hydrogen-bonding interaction (Scheme 7.29).



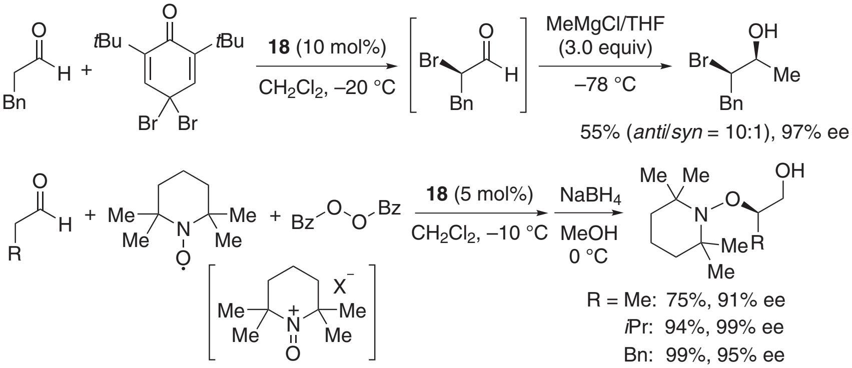
Scheme 7.29 Enantioselective hydroxyamination of aldehydes.

Such bifunctional catalysis by a chiral secondary amino alcohol catalyst is also effective for the direct asymmetric iodination of aldehydes with *N*-iodosuccinimide, in which a slightly modified catalyst [**17b** with a bis(pentafluorophenyl) hydroxymethyl group] displayed remarkable catalytic and chiral efficiencies (Scheme 7.30) [53].



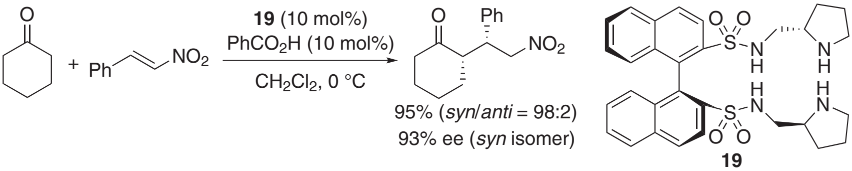
Scheme 7.30 Direct asymmetric iodination of aldehydes.

On the other hand, however, trimethylsilyl-protected catalyst **18** was suitable for the asymmetric bromination of aldehydes, and the resulting α-bromoaldehydes can be diastereoselectively transformed into the corresponding bromohydrin in one-pot (Scheme 7.31) [54]. An additional utility of catalyst **18** was highlighted by application to the development of the direct aminoxylation of aldehydes with an oxoammonium salt generated from 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) by *in situ* oxidation with benzoyl peroxide, allowing for the highly enantioselective synthesis of stable α-aminoxy aldehydes, which could subsequently be reduced to the corresponding alcohol [55].



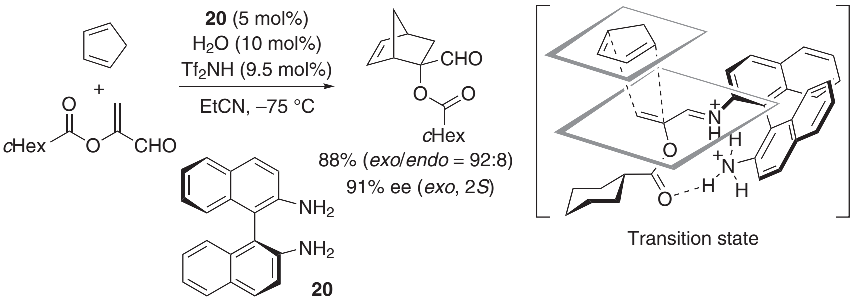
Scheme 7.31 Enantioselective α-functionalization of aldehydes catalyzed by **18.**

As a novel type of proline-based secondary amine, Du devised the chiral binaphthyl bis-sulfonamide **19** and demonstrated that it could act as an efficient catalyst for the asymmetric Michael addition of cyclohexanone to nitrostyrene, giving rise to the corresponding γ-nitroketone derivative with high levels of diastereo- and enantioselectivity (Scheme 7.32) [56].



Scheme 7.32 Catalysis by proline-based chiral bis-sulfonamide **19.**

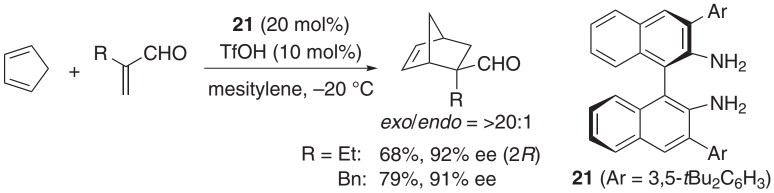
In 2006, Ishihara showed that a diammonium salt of commercially available chiral (*S*)-2,2′-diamino-1,1′-binaphthalene (**20**) and bis(trifluoromethane)sulfonimide (Tf_2NH) exhibited excellent catalytic activity and stereoselectivity in the Diels–Alder reaction of α-acyloxyacroleins with cyclic dienes (Scheme 7.33) [57].



Scheme 7.33 Chiral diamine-catalyzed Diels–Alder reaction.

The formation of strong intramolecular hydrogen bonding between the acyl group and the protonated amine moiety of the catalyst in the transition state (Tf_2N^- omitted) would be a key for attaining high selectivity. Acyclic dienes were also employable, although a certain decrease of enantioselectivity was observed.

Maruoka also utilized 3,3′-modified binaphthyl-derived chiral primary amine **21**, in combination with trifluoromethanesulfonic acid (TfOH), as a catalyst for the Diels–Alder reaction of α-substituted α,β-unsaturated aldehydes with cyclopentadiene, which afforded the corresponding cycloadducts possessing an all-carbon quaternary stereocenter with good to high stereoselectivity (Scheme 7.34) [58].

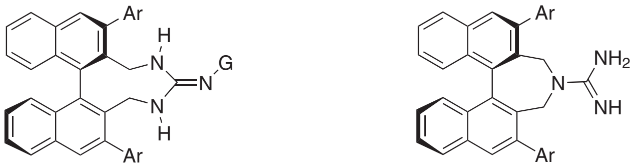


Scheme 7.34 Performance of 3,3′-modified **21** in a Diels–Alder reaction.

7.5
Chiral C_2-Symmetric Brønsted Bases: Guanidines

A series of structurally intriguing, chiral C_2-symmetric guanidines have been introduced by Terada (Figure 7.4), and his group has been carrying out extensive studies on demonstrating the vast potential of this class of relatively strong organic base catalyst.

To overcome the difficulty associated with the design of chiral guanidines as a catalyst, the binaphthyl-derived **22** was initially developed with the expectation that substituents at the 3,3′-positions of the binaphthyl backbone would break the planar symmetry of the guanidine skeleton to create an attractive chiral environment. This type of axially chiral organic base catalyst, particularly **22a**, could indeed

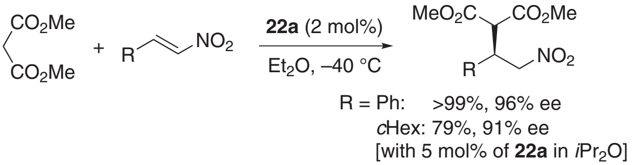


22a (G = Me, Ar = 3,5-(3,5-tBu$_2$C$_6$H$_3$)$_2$C$_6$H$_3$)
b (G = Ph$_2$CH, Ar = 3,5-tBu$_2$C$_6$H$_3$)
c (G = (3,4,5-(MeO)$_3$C$_6$H$_2$)$_2$CH, Ar = Ph)

23 (Ar = 4-(3,5-tBu$_2$C$_6$H$_3$)C$_6$H$_4$)

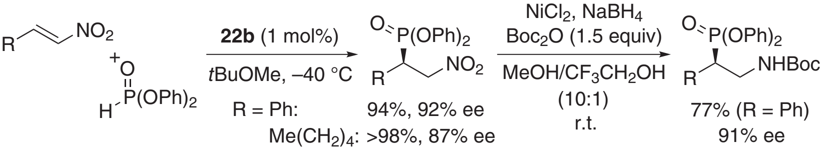
Figure 7.4 Axially chiral C_2-symmetric guanidines.

promote the highly enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes as illustrated in Scheme 7.35 [59].



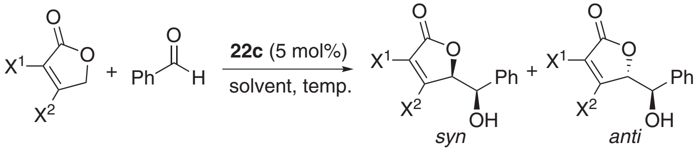
Scheme 7.35 Conjugate addition of malonate to nitroalkenes.

A chiral guanidine catalyst of type **22** was then successfully utilized to tackle unsolved methodological challenges. For instance, **22b** was found to catalyze the conjugate addition of diphenyl phosphite to various nitroalkenes with high levels of enantioselectivity, providing a straightforward route to optically active β-amino phosphonate derivatives of biological and pharmaceutical importance (Scheme 7.36) [60].

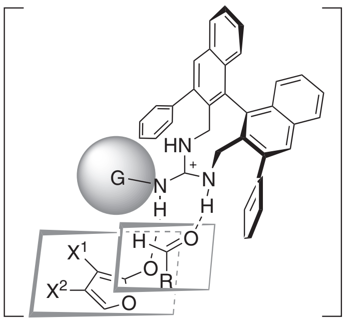


Scheme 7.36 Conjugate addition of diphenyl phosphite.

Moreover, the stereoselective, direct vinylogous aldol reaction of halogenated or α-thio-substituted furanones with aldehydes was achieved by using appropriately tuned **22c** as an optimal catalyst (Scheme 7.37) [61]. On the basis of analyses of the absolute configurations of the products as well as the relationship between the catalyst structure and the stereochemical outcomes, a transition state model was proposed. In this model, furanone-derived enolate would be located close to the



X^1	X^2	solvent	temp.	yield	*syn*/*anti*	ee (*syn*)	ee (*anti*)
Cl	Cl	THF	–40 °C	90%	77:23	99%	87%
Br	Br	acetone/THF (1:1)	–40 °C	77%	90:10	98%	84%
PhS	H	acetone/THF (1:1)	–80 °C	>99%	85:15	>99%	91%

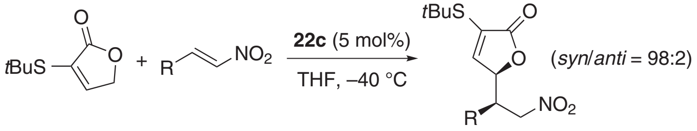


Transition state model

Scheme 7.37 Direct vinylogous aldol reaction.

G-substituent of the catalyst and the aldehyde would approach from the far side of this diarylmethyl group, while keeping away from the phenyl substituent of the binaphthyl backbone. Since the enolate would be oriented to minimize the steric repulsion of C4 halogen atom with aldehyde substituent, it was most likely that the *Si* face of the aldehyde was attacked by the *Si* face of the furanone enolate to give the 1′*R*-configured *syn* product as experimentally observed.

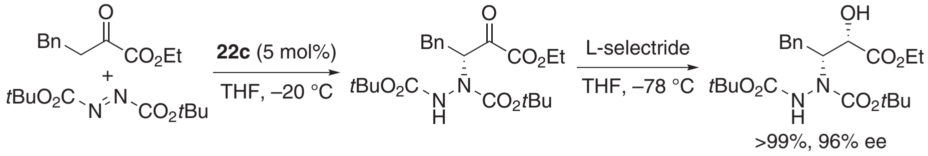
Under the catalysis of **22c**, a structurally similar pro-nucleophile, α-*tert*-butylthio-substituted furanone, underwent the highly *syn*- and enantioselective vinylogous Michael addition to nitroalkenes (Scheme 7.38) [62]. These methods allowed facile access to optically active polyfunctionalized butenolides, which are versatile chiral synthons in organic synthesis.



R = Ph: 76%, 94% ee
4-MeOC$_6$H$_4$: 77%, 88% ee
4-BrC$_6$H$_4$: 65%, 94% ee

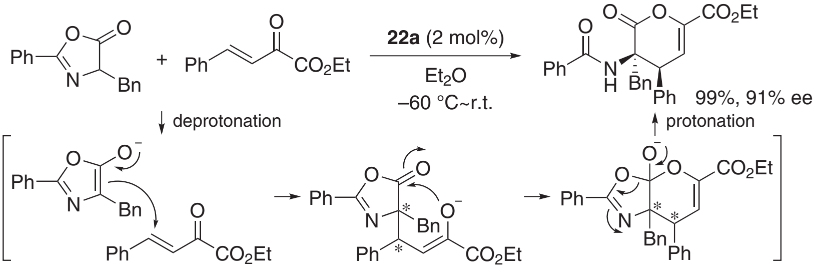
Scheme 7.38 Vinylogous Michael addition.

The catalyst **22c** was also effective for the enantioselective β-functionalization of α-ketoesters with azodicarboxylates to prepare enantioenriched β-hydrazinyl-α-ketoesters (Scheme 7.39) [63].



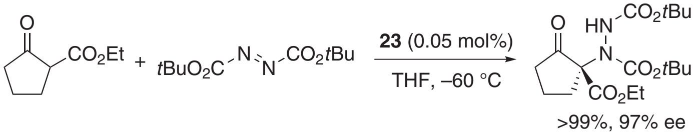
Scheme 7.39 Enantioselective amination of α-ketoesters.

On the other hand, **22a** bearing sterically demanding aromatic substituents on the binaphthyl unit and the small methyl group on the guanidine nitrogen turned out to be a catalyst of choice for the [4+2] cycloaddition of azlactone to β,γ-unsaturated α-ketoesters, which proceeded through three consecutive transformations to afford α-amino-δ-lactone derivatives with high diastereo- and enantioselectivities (Scheme 7.40) [64].



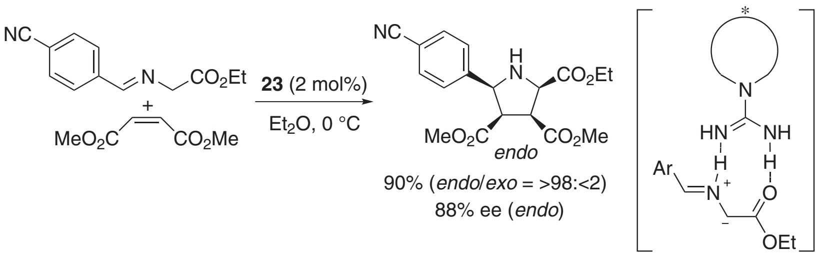
Scheme 7.40 [4+2] cycloaddition.

The structurally related, chiral guanidines **23** with a seven-membered ring framework was designed by Terada on considering the C_2-symmetric structure of the protonated guanidinium ions. This new family of chiral guanidine bases was initially evaluated in the asymmetric electrophilic amination of α-monoalkyl 1,3-dicarbonyl compounds, revealing that the bulky 3,3′-substituents were critical in realizing high catalytic activity and enantioselectivity (Scheme 7.41) [65].



Scheme 7.41 Performance of **23** in the asymmetric amination of β-ketoesters.

The application of **23** to the enantioselective [3+2] cycloaddition of dimethyl maleate with glycinate Schiff bases established a protocol for the preparation of pyrrolidine derivatives in a stereoselective fashion, where the acid–base dual function of the catalyst through the double hydrogen-bonding interaction was crucial for gaining substantial acceleration of the reaction (Scheme 7.42) [66].



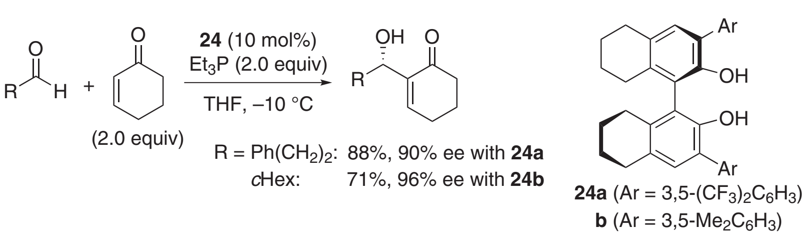
Scheme 7.42 Enantioselective [3+2] cycloaddition.

By installing aromatic substituents of suitable steric and electronic properties, this type of chiral guanidine catalyst could find numerous applications in asymmetric synthesis [67].

7.6
Chiral C_2-Symmetric Brønsted Acids

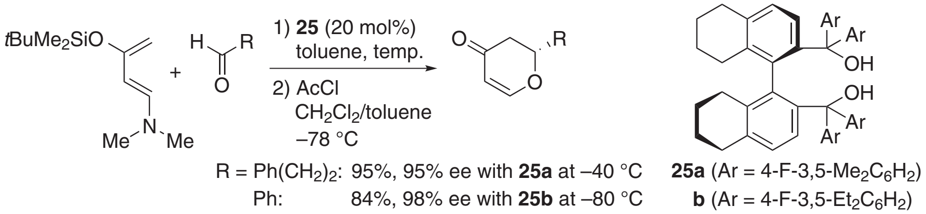
7.6.1
Binaphthol and Biphenol Derivatives

The ability of chiral binaphthol (BINOL) derivatives as a Brønsted acid catalyst to facilitate asymmetric transformations was demonstrated by Schaus by the development of the highly enantioselective Morita–Baylis–Hillman reaction of cyclohexenone with aldehydes effectively catalyzed by (*R*)-octahydro-1,1′-bi-2-naphthol derivatives, bearing either 3,5-bis(trifluoromethyl)phenyl (**24a**) or 3,5-xylyl (**24b**) groups at the 3,3′-positions, in combined use with triethylphosphine as a nucleophilic promoter (Scheme 7.43) [68].


24 (10 mol%)
Et₃P (2.0 equiv)
THF, −10 °C
(2.0 equiv)
R = Ph(CH₂)₂: 88%, 90% ee with 24a
cHex: 71%, 96% ee with 24b
24a (Ar = 3,5-(CF₃)₂C₆H₃)
b (Ar = 3,5-Me₂C₆H₃)

Scheme 7.43 Brønsted acid catalysis of **24** for the Morita–Baylis–Hillman reaction.

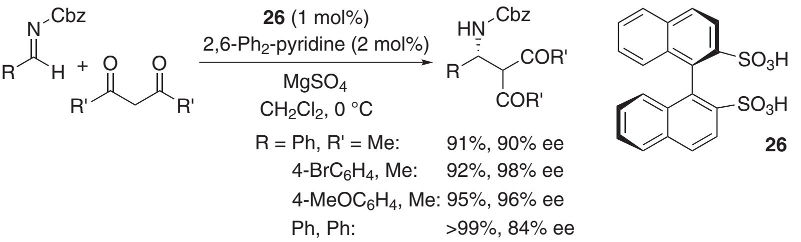
Rawal and Yamamoto visualized that axially chiral 1,1′-biaryl-2,2′-dimethanols (BAMOLs) **25a** and **25b** possessing the 4-fluoro-3,5-dimethylphenyl and 4-fluoro-3,5-diethylphenyl groups, respectively, could activate the aldehyde carbonyl through hydrogen bonding and thus act as a prominent catalyst for the enantioselective hetero-Diels–Alder reaction of an aminosiloxydiene with a wide variety of aldehydes as illustrated in Scheme 7.44 [69].



Scheme 7.44 Chiral diol **25** for the hetero-Diels–Alder reaction.

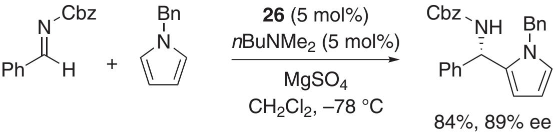
7.6.2
Pyridinium Disulfonates

In 2008, Ishihara established a practical procedure for the synthesis of optically active, chiral 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA) (**26**) from BINOL, and also showed that *in situ*-generated **26**–2,6-diphenylpyridine (1 : 2) salts behaved as an efficient enantioselective catalyst in the direct Mannich-type reaction of 1,3-diketones with aromatic aldimines (Scheme 7.45) [70, 71].


N
Cbz
R
H
+
O
O
R'
R'
26 (1 mol%)
2,6-Ph2-pyridine (2 mol%)
MgSO4
CH2Cl2, 0 °C
HN
Cbz
R
COR'
COR'
R = Ph, R' = Me: 91%, 90% ee
4-BrC6H4, Me: 92%, 98% ee
4-MeOC6H4, Me: 95%, 96% ee
Ph, Ph: >99%, 84% ee
SO3H
SO3H
26

Scheme 7.45 Catalysis of chiral Brønsted acid–base combined salt.

This approach provided a flexible strategy for identifying an optimal catalyst for a given transformation by taking advantage of the dynamic nature of the salt formation between **26** and easily tunable Brønsted bases. For example, a simple survey of various tertiary amines in combination with **26** in the Friedel–Crafts aminoalkylation between aromatic aldimines and *N*-benzylpyrrole made it feasible to rapidly single out the **26**–*N*,*N*-dimethylbutylamine (1 : 1) salt as the most reactive and enantioselective catalyst (Scheme 7.46) [72].



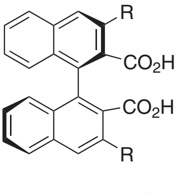
Scheme 7.46 Friedel–Crafts aminoalkylation.

7.6.3
Dicarboxylic Acids

While carboxylic acids have been recognized as one of the most promising acid catalysts in organic synthesis, they had been scarcely utilized for asymmetric Brønsted acid catalysis. This situation was presumably due to the relatively poor reactivity of the carboxylic acid and the difficulty associated with creating a discrete chiral environment around the acidic functionality. Maruoka addressed this problem by designing chiral 1,1′-binaphthyl-2,2′-dicarboxylic acid derivatives **27** (Figure 7.5).

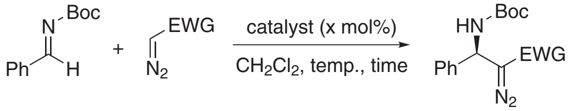
Interestingly, **27a** exerted much higher catalytic efficiency than that of 2-naphthoic acid in the Mannich-type reaction of benzaldehyde *N*-Boc imine and *tert*-butyl diazoacetate, although no appreciable asymmetric induction was detected. Introduction of an appropriate aromatic group to the 3,3′-positions of the binaphthyl backbone was beneficial in terms of attaining sufficient enantioselectivity and the use of molecular sieves (4Å) as a scavenger of the adventitious water, which would cause imine hydrolysis, was crucial for obtaining the product in a synthetically useful chemical yield. The generality of this catalytic method was demonstrated by extending it to reactions with (diazomethyl)phosphonate and (diazomethyl)sulfone, from which highly enantioenriched chiral β-amino phosphonates and β-amino sulfones could be obtained (Scheme 7.47) [73].

On the basis of observations from an X-ray crystallographic analysis of the 1 : 1 complex of **27b** and 4-pyrrolidinopyridine, a transition-state model of the Mannich-type reaction was postulated (Scheme 7.47) [73b]. *N*-Boc imine would be activated by one of the two carboxyl acids in **27b** and the steric hindrance of 3,3′-substituents and the binaphthyl moiety would restrict rotation of the O···H–N hydrogen bond, thus regulating the conformational orientation of the imine. Then,

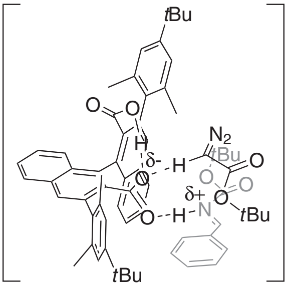


27a (R = H)
b (R = 2,6-Me_2-4-*t*BuC_6H_2)
c (R = 2,4,6-$Me_3C_6H_2$)
d (R = 2,6-Me_2-4-(1-Ad)C_6H_2)
e (R = $SiMePh_2$)
f (R = CH(2-Np)$_2$)

Figure 7.5 Axially chiral C_2-symmetric dicarboxylic acids.



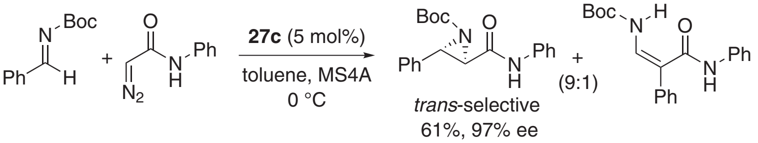
EWG	catalyst	x	MS4A	temp.	time	yield	ee
CO_2tBu	2-$NpCO_2H$	20	|	r.t.	40	3%	|
CO_2tBu	**27a**	10	|	r.t.	20	33%	0%
CO_2tBu	**27b**	5	|	0 °C	38	38%	95%
CO_2tBu	**27b**	5	○	0 °C	24	80%	95%
$PO(OMe)_2$	**27b**	5	○	0 °C	85	68%	96%
SO_2Tol	**27b**	5	○	0 °C	70	70%	92%



Scheme 7.47 Chiral dicarboxylic acid-catalyzed Mannich-type reactions.

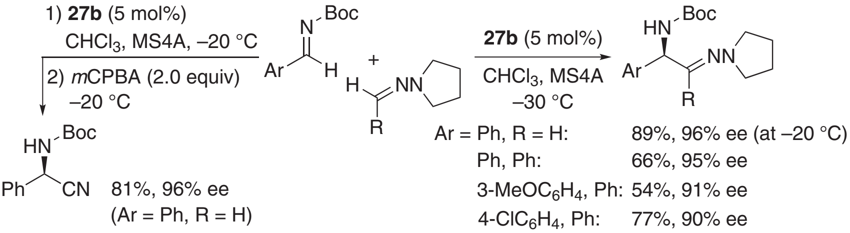
the nucleophilic diazoacetate approached from the side of the inward oxygen acting as a Lewis base through the initial formation of a hydrogen bond with the α-hydrogen of the diazoacetate.

The reaction of *N*-Boc imines with diazoacetamides under catalysis of this class of chiral Brønsted acid did not give a Mannich-type adduct but afforded an aziridine with complete trans selectivity, and **27c**, having 2,4,6-trimethylphenyl (mesityl) substituents, was identified as an optimal catalyst for realizing rigorous enantiocontrol (Scheme 7.48) [74].



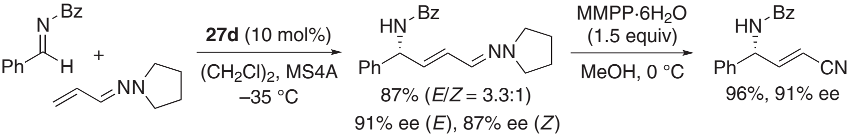
Scheme 7.48 Aziridination of diazoacetamides and *N*-Boc imines.

The axially chiral dicarboxylic acid **27b** was also uniquely reactive in achieving the highly enantioselective addition of aldehyde *N,N*-dialkylhydrazones, a readily available acyl anion equivalent, to *N*-Boc imines (Scheme 7.49) [75]. Notably, this system tolerated the employment of arylaldehyde *N*,*N*-dialkylhydrazones as a nucleophilic reaction partner. The synthetic potential of the **27b**-catalyzed asymmetric imino aza-enamine reaction of formaldehyde *N*,*N*-dialkylhydrazones with *N*-Boc imines was demonstrated by combination with the single-pot oxidation of the *N*,*N*-dialkylhydrazone moiety. This overall process served as a useful alternative of asymmetric Strecker reaction as included in Scheme 7.49 [76].



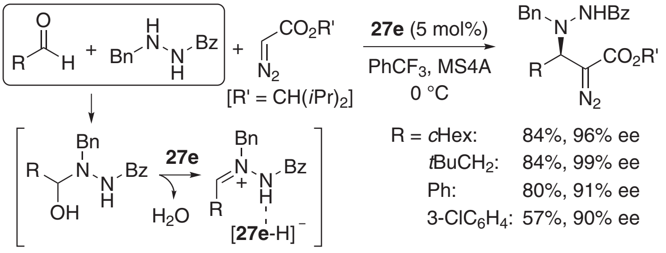
Scheme 7.49 Imino aza-enamine reaction.

Furthermore, the asymmetric catalysis of **27** could accommodate vinylogous aza-enamines as a source of an alkenyl unit, and the use of **27d** bearing the 2,6-dimethyl-4-(1-adamantyl)phenyl groups as catalyst led to the establishment of the general and highly enantioselective formal alkenylation of *N*-benzoyl imines [77]. Since the oxidative transformation of an aza-enamine moiety of the product into a nitrile functionality appeared feasible as described above, this method offered facile access to optically active γ-amino α,β-unsaturated nitriles (Scheme 7.50).



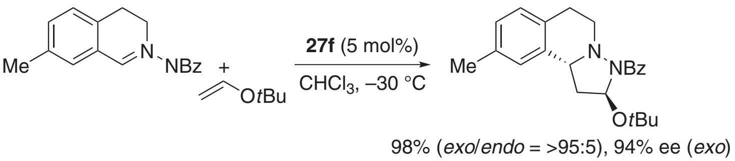
Scheme 7.50 Formal alkenylation of imines with vinylogous aza-enamines.

An additional salient feature of **27** as a chiral Brønsted acid catalyst was its ability both to generate *in situ* a protonated acyclic azomethine imine from an aldehyde and *N*′-benzylbenzoylhydrazide and to control the absolute stereochemistry in the subsequent reaction with a mild nucleophile such as diazoacetates (Scheme 7.51) [78]. A key for inducing a high level of enantiocontrol in this previously elusive yet synthetically valuable catalytic system was the employment of 3,3′-diphenylmethylsilyl-substituted **27e** as a catalyst.



Scheme 7.51 Generation and utilization of acyclic azomethine imines.

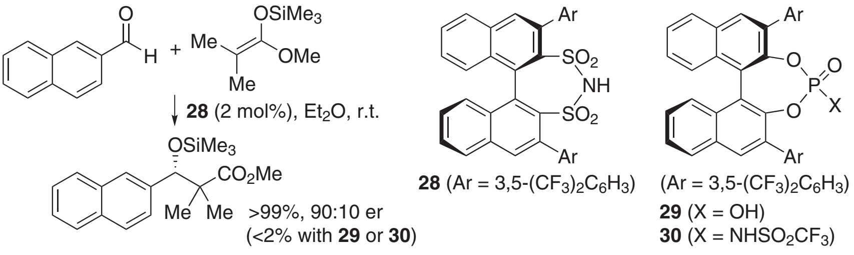
The use of **27f**, with bis(2-naphthyl)methyl groups at the 3,3′-positions, as a catalyst enabled the employment of *C,N*-cyclic azomethine imines as a dipole for the asymmetric inverse-electron-demand 1,3-dipolar cycloaddition with vinyl ethers as exemplified in Scheme 7.52 [79].



Scheme 7.52 1,3-Dipolar cycloaddition of *C,N*-cyclic azomethine imines.

7.6.4
Chiral Disulfonimides

In 2009, List introduced a binaphthyl-derived, chiral disulfonimide (**28**) as a new structural motif of a powerful chiral Brønsted acid that could activate simple aldehydes [80, 81]. Evaluation of the catalytic activity and stereocontrolling ability of **28** in the Mukaiyama aldol reaction of silyl ketene acetal with naphthaldehyde revealed that **28** was not only far more reactive than phosphoric acid **29** and phosphoramide **30** but also capable of affording the aldol product with high enantioselectivity (Scheme 7.53).



Scheme 7.53 Chiral disulfonimide as catalyst for the Mukaiyama aldol reaction.

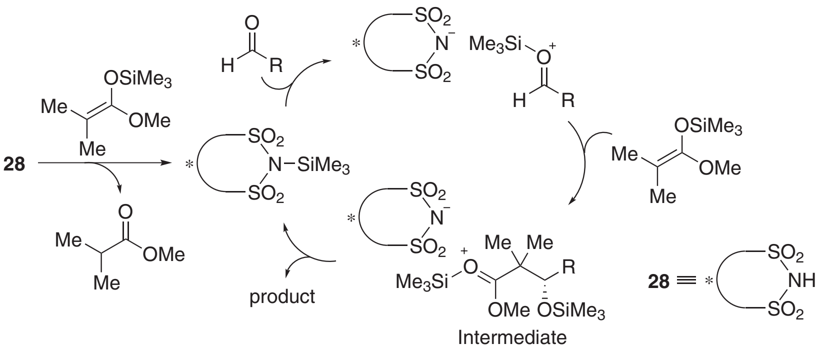
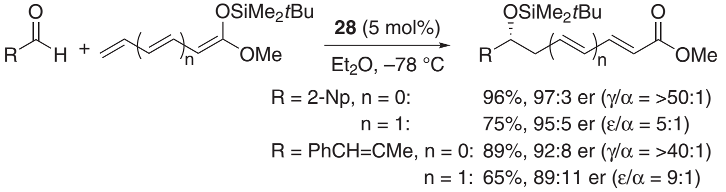


Figure 7.6 Catalytic cycle proposed for the aldol reaction.

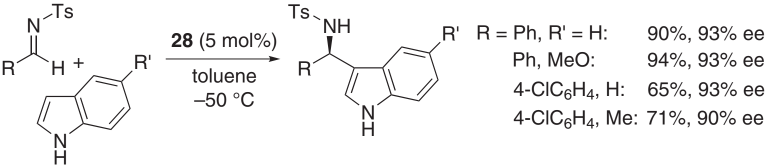
While catalyst **28** may directly protonate the aldehyde to form an ion pair, an alternative yet more likely mechanism was proposed (Figure 7.6). The initial silylation of **28** by ketene silyl acetal may occur to form an *N*-silyl disulfonamide that could then activate the aldehyde as an actual catalyst through silyl transfer to generate an *O*-silylated oxonium cation paired with disulfonimide anion. Therefore, the stereochemical outcome would be determined in the reaction of this ion pair with silyl ketene acetal to give the product through the intermediate shown in Figure 7.6.

This system based on the catalysis of **28** was extended to the development of vinylogous and bis-vinylogous Mukaiyama aldol reactions, which displayed good to excellent enantioselectivity and broad applicability with respect to silyl ketene acetals of higher vinylogy (Scheme 7.54) [82].


O
R
H
+
n
OSiMe2tBu
OMe
28 (5 mol%)
Et2O, −78 °C
OSiMe2tBu
O
R
n
OMe
R = 2-Np, n = 0: 96%, 97:3 er (γ/α = >50:1)
n = 1: 75%, 95:5 er (ε/α = 5:1)
R = PhCH=CMe, n = 0: 89%, 92:8 er (γ/α = >40:1)
n = 1: 65%, 89:11 er (ε/α = 9:1)

Scheme 7.54 Vinylogous and bis-vinylogous Mukaiyama aldol reaction.

On the other hand, Lee showed that **28** could activate *N*-sulfonyl imines through hydrogen-bonding interaction and could function as an efficient Brønsted acid catalyst for the highly enantioselective Friedel–Crafts alkylation of indoles with the imines (Scheme 7.55) [83]. It was essential to wash the catalyst with dilute hydrochloric acid followed by water and brine prior to use to attain sufficient reactivity.

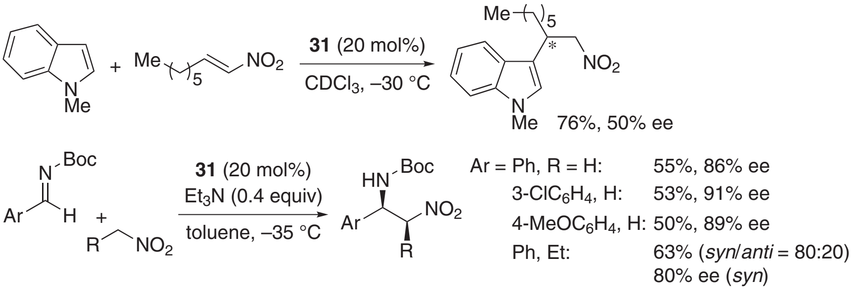


Scheme 7.55 Asymmetric Friedel–Crafts alkylation of indoles with imines.

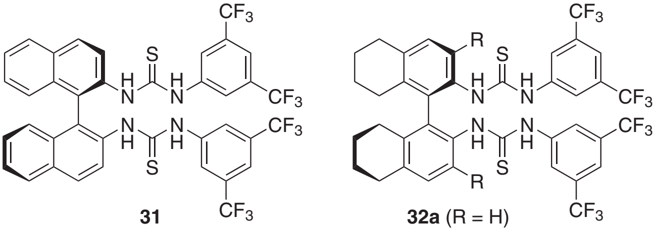
7.7
Chiral C_2-Symmetric Bis-Thioureas

Along with the remarkable progress in the development of catalytic asymmetric transformations by means of chiral thioureas as a hydrogen-bonding donor catalyst, axially chiral, C_2-symmetric bis-thioureas **31** and **32** (Figure 7.7) have been elaborated and utilized as activators of electrophiles through hydrogen-bonding interaction, often in the context of synergistic catalysis with an appropriate organic base.

Connon introduced binaphthyl-derived bis-thiourea **31** and demonstrated that it could catalyze the addition of *N*-methylindole to various nitroalkenes, including those incorporating β-aliphatic substituents, although the enantioselectivity was generally moderate (Scheme 7.56) [84]. The utility of **31** was also proven by Wulff through use with a sub-catalytic amount of triethylamine for stereoselectively facilitating the aza-Henry reaction of nitroalkanes with *N*-Boc imines [85].



Scheme 7.56 Performance of **31** in Friedel–Crafts alkylation and aza-Henry reaction.

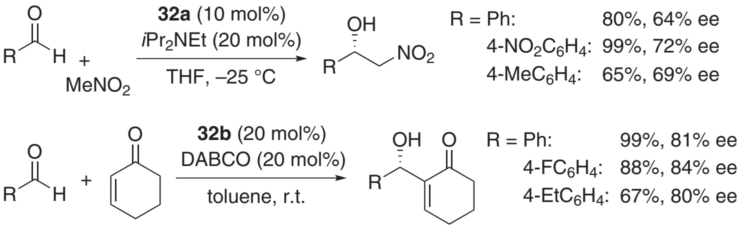


31

32a (R = H)
b (R = 3,5-$(CF_3)_2C_6H_3$)

Figure 7.7 Axially chiral C_2-symmetric bis-thioureas.

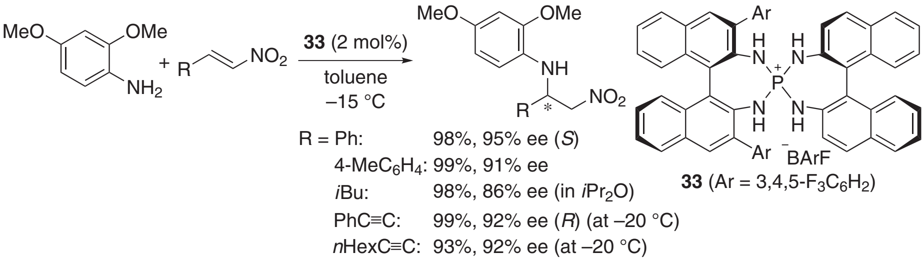
The synthetic route to the structurally related bis-thioureas of type **32** from (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine was reported by Shi. The effectiveness of the acid–base synergistic catalysis of parent **32a** and *N*,*N*-diisopropylethylamine was verified by application to the asymmetric Henry reaction of nitromethane with aromatic aldehydes (Scheme 7.57) [86]. Moreover, the Morita–Baylis–Hillman reaction between 2-cyclohexen-1-one or 2-cyclopenten-1-one and aromatic aldehydes was found to proceed with moderate to good levels of enantioselectivity under the catalysis of **32b**, which has additional 3,5-bis(trifluoromethyl)phenyl groups at the 3,3′-positions of the octahydrobinaphthyl backbone, and 1,4-diazabicyclo[2.2.2]octane (DABCO) (Scheme 7.57) [87].



Scheme 7.57 Effectiveness of **32** in Henry and Morita–Baylis–Hillman reactions.

7.8 Chiral C_2-Symmetric Aminophosphonium Ions

During our continuous efforts to expand the potential of chiral tetraaminophosphonium salts as organic molecular catalysts, we designed and synthesized heterochiral, [7.7]-*P*-spirocyclic arylaminophosphonium barfates of type **33** as a novel charged, cationic Brønsted acid catalysts. Their catalytic and stereocontrolling abilities were clearly demonstrated in the development of the highly enantioselective conjugate addition of arylamines to nitroolefins (Scheme 7.58) [88a]. This system could be successfully extended to the aza-Michael addition to conjugated nitroenynes [88b].



Scheme 7.58 Arylaminophosphonium ions as a cationic Brønsted acid catalyst.

7.9
Summary and Conclusions

In the remarkable evolution of asymmetric organic molecular catalysis, a wide variety of axially chiral, C_2-symmetric acid, base, and nucleophilic/Lewis basic catalysts featuring appropriately substituted biaryl structures have been developed and have found significant synthetic utilities. Meanwhile, catalysts that possess a relatively underutilized, axially chiral backbone such as allenes and spirocycles have emerged, exerting promising catalytic and chiral efficiencies. As is probably evident from this chapter, the development and applications of this class of organocatalyst have been creating a rich stream of research, and further efforts towards the molecular design of essentially new catalysts of this category and a deeper understanding of the relationship between their structures and reactivity and stereoselectivity would greatly expand the potential of such asymmetric organocatalysis.

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8
Planar Chiral Catalysts

Olivier R.P. David

8.1
Introduction

In the Cahn–Ingold–Prelog (CIP) system three stereogenic units are accepted, namely, the center, axis, and plane [1]. Molecules presenting planar chirality [2] were first described in 1941 [3] with the report of "ansa compounds," which in fact are seminal examples of chiral dioxaparacyclophanes in enantiopure form. After leaving behind their status of laboratory curiosities and concept-challenging examples of the definition of stereoisomerism, such compounds have found applications in theoretical chemistry, material science, supramolecular chemistry, and more recently in catalysis. If cyclophanes were the first, and still the most, reported organic structures with planar chirality, best exemplified by substituted [2.2]paracyclophanes, other molecular scaffolds possess this property, such as metal complexes of arenes, epitomized by disubstituted ferrocenes;[1] annulenes, and *trans*-cycloalkenes [4]. As molecular architectures with particular arrangements in space they can create strongly differentiated facial environments around a reactive center, which explains why these scaffolds are used in the design of efficient chiral catalysts. Planar chirality was first used in metallocatalysis [5] with phosphorus-based ligands, but applications then extended to organocatalysis with the planar chiral flavine-based oxidation reported by Shinkai [6] in 1988. In this chapter we examine the different scaffolds featuring planar chirality that have been used in enantioselective organocatalysis. In the first part, Lewis bases will be presented according to the nature of the atom bearing the active electronic pair: nitrogen, oxygen, phosphorus, carbon, or sulfur. Then, promoters relying on electrophilic activation, either with Lewis acidic or H-bonding moieties, will be covered. Finally, we will examine redox-active structures used in biomimetic reductions/oxidations.

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1) Conceptually, the chirality of substituted metallocene can be treated by following the rules for compounds with "centred chirality" (see Reference [5]) by considering each substituted position of the plane as a stereogenic center. However, in this chapter we will still consider the whole substituted ferrocene structure as "planarly chiral."

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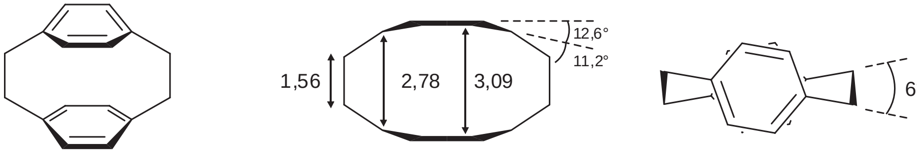


Figure 8.1 Structure and selected angles and distances in [2.2]paracyclophane.

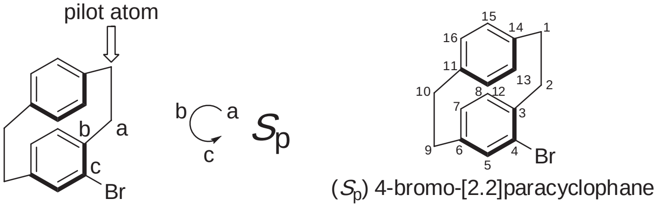


Figure 8.2 Stereochemical assignation and numbering of bromo-[2.2]paracyclophane.

As most of the catalysts presented here are derived from either [2.2]paracyclophane or ferrocene, we will briefly detail some useful structural characteristics as well as elements of nomenclature about these derivatives. Figure 8.1 shows [2.2] paracyclophane (Pc) [7], which displays an abnormally short phenyl–phenyl ring distance. Hence the *para* positions are separated by only 2.78 Å, with ring centers being 3.09 Å apart, whereas stacked aromatics are usually 3.40 Å apart. To prevent a totally eclipsed conformation between the facing benzylic positions, aromatic rings are constantly rotating one relative to the other, inducing a twist of ca 6°. Altogether, inherent strain within Pc derivatives results in a relative conformational "stiffness" and, thus, in well-defined and predicable shapes. The presence of one substituent breaks the initial D_{2h} symmetry of paracyclophane and renders the molecule chiral. For chiral derivatives, assignment of the absolute configuration and numbering rely on a specific nomenclature (Figure 8.2). One has first to determine the "pilot" atom as the nearest atom out of the chiral plane. The latter is the plane bearing the atom with the highest priority according to the CIP rules among the two aromatics; in this example, the chiral plane is the bottom one. Subsequently, the pilot atom is chosen as the first one encountered when leaving this chiral plane and which is the closest to the atom with the highest CIP priority; here the methylene carbon atom of the top plane, and on the right-hand side, closer to the bromo substituent. The pilot atom is then the "point-of-view" from which to determine the absolute configuration of the compound. From this location, one's eye considers the next atom belonging to the chiral plane (atom noted a), and follows the path from there to the atom with the highest CIP priority, atoms noted b and c. The descriptor is then assigned according to the direction of circulation a-b-c viewed from the pilot atom; here it is counterclockwise from the bottom benzylic position to the bromine atom, leading to a (S_p) configuration. Complete numbering then follows the same circulation; see right-hand structure on Figure

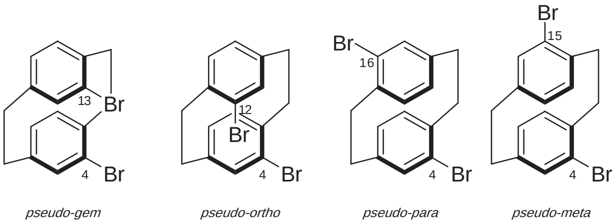


Figure 8.3 Prefixes employed for paracyclophanes.

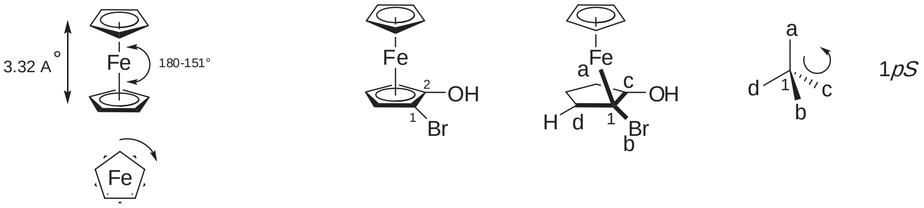


Figure 8.4 Structural features of ferrocene.

8.2. If one now considers disubstituted Pc derivatives, particular descriptors are employed to designate the relation between the two positions. For substituents on the same phenyl ring, *ortho, meta,* and *para* prefixes are still valid, while inter-ring disubstitution gives rise to *pseudo-gem, pseudo-ortho, pseudo-para,* and *pseudo-meta* prefixes (Figure 8.3). Finally, a last remark about the configurational stability of Pc derivatives: chiral [2.2]paracyclophanes can indeed racemize above 200 °C by a process that was proven to involve benzylic-bond homolytic scission, rotation, and recombination of the diradical.

Ferrocene (Fc) (Figure 8.4) also features two parallel aromatic rings linked by an iron atom, but the sandwich-like structure leads to a much more flexible compound compared to Pc. Hence, the two cyclopentadienyl rings freely rotate, one relative to the other, introducing total torsional freedom [8]. Moreover, if the most probable angle for the central axis Cp–Fe–Cp is 180 °, conformational deformation can lead to axis bending with angle values down to 151 °. This rather large conformational flexibility must be taken into account in catalyst design, since ferrocene Cp rings can easily deviate from parallelism and thus modify the expected facial encumbrance. Stereochemical assignation relies on a slightly modified classical determination for tetrahedral stereogenic centers [9]. In metallo-arenes, each atom of the disubstituted ring is considered stereogenic, and the absolute configuration of the whole compound is inferred from the configuration of the aromatic position bearing the substituent with the highest CIP priority, which is thus attributed the numbering 1. The four neighboring atoms are classically ranked a-b-c-d, according to CIP rules, then circulation of a-b-c after placing d *anti* to the observer gives the descriptor. In the example depicted on Figure 8.4, atom 1 is substituted by a bromine atom and thus possesses a (p*S*) configuration and the compound is denominated (p*S*)-1-bromo-2-hydroxyferrocene. Complete attribution would deliver (1*S*,2*R*,3*R*,4*S*,5*S*) descriptors.

Having considered these structural details we now turn to the electronic properties of ferrocene. As cyclopentadienyl rings are at least formally anionic in nature, they display strong electron-donating ability; this is much in contrast with a phenyl ring, which is slightly electron withdrawing. As an illustration, one can compare the electrophilicity (*E*) of three cations according to Mayr: PhCH$^+$Ph 5.30, FcCH$^+$Ph –2.64, and FcCH$^+$Fc –8.54 (the lower the value of *E* the more stabilized the species) [10]. For the same reason, ferrocene itself can undergo facile S_EAr reactions.

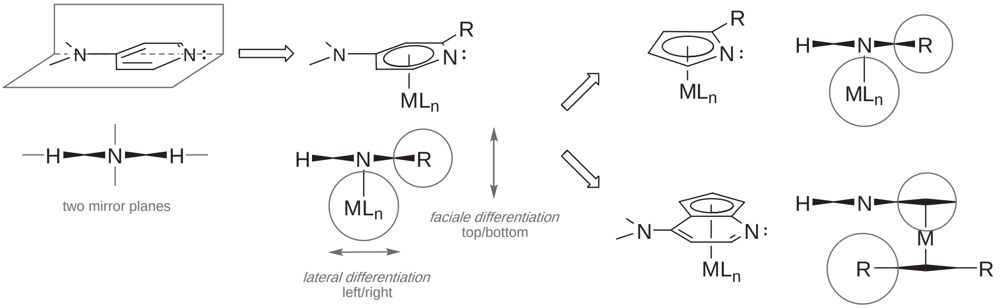
Now that we are familiar with common planar chiral backbones, we can examine functionalized derivatives that were shown to exhibit catalytic activity with non-negligible levels of stereoinduction.

8.2
Lewis/Brønsted Bases

As the most represented mode of activation in organocatalysis to-date, we begin with catalysts acting as Lewis bases. Following Denmark's recommendation [11], the activation mode and catalyst itself are designated as Lewis basic, with the terms nucleophilic/electrophilic being employed to specify the properties of the reactive intermediate.

8.2.1
Nitrogen Bases

In 1996 Fu and Ruble [12] reported the first study of ferrocene derivatives fitted with a trigonal nitrogen atom acting as a Lewis base. Interestingly, in this seminal work, the two main families of "planar chiral DMAP" were introduced, namely, azaferrocenes and pyridinoferrocenes. These studies resulted in the development of an impressive number of innovative transformations and these advances have been reviewed in several contributions [13]. The underlying concept at the basis of the stereoselection, presented in Scheme 8.1, relies on the "symmetry breaking"



Scheme 8.1

of DMAP [4-(dimethylamino)pyridine]. Proper substitution of the pyridine ring eliminates the two mirror planes present in DMAP and thus renders such compounds good candidates in enantioselective reactions due to strong facial and lateral differentiations within the reactive intermediate. Hence, substitution at the 2-position of pyridine introduces a steric encumbrance resulting in a preferential left/right orientation of the reactive moiety attached to the nitrogen atom. Then, π-complexation of the pyridine to a metal breaks the last symmetry element and renders the whole architecture planar chiral while strongly differentiating the two faces of the reactive intermediate. Such a design is not applicable to DMAP itself – the 19-electron complex hence formed was deemed too unstable to be used as catalyst. Two classes of compounds were thus conceived by modification of the original design in order to comply with the necessary catalyst robustness (18-electon complexes). Pyrrolide-derived π-complexes meet these requirements, giving rise to azaferrocenes as first candidates, while shifting the ferrocenic moiety to the side of DMAP results in a second family of compounds. The latter modification has consequences for facial discrimination; since the bulky metal center is removed from the vicinity of the nitrogen, the steric demand under the pyridine plane must now be assured by the bottom arene, much like an umbrella protection. The preparation and important properties of these two classes of compounds will now be detailed.

8.2.1.1 **Azaferrocenes**

Figure 8.5 depicts the different chiral azaferrocene derivatives synthesized and used in catalysis. The first member in the series bears a TES protected hydroxymethyl group and was prepared in optically pure form in three steps, including a preparative HPLC enantiomer separation (Scheme 8.2) [11]. Optimization studies later showed the greater stereoinduction brought about by bulkier silyl groups, with the TBS-substituted derivative achieving 77% ee for the addition reaction of methanol to methyl phenyl ketene, whereas the TES derivative shows only 28%

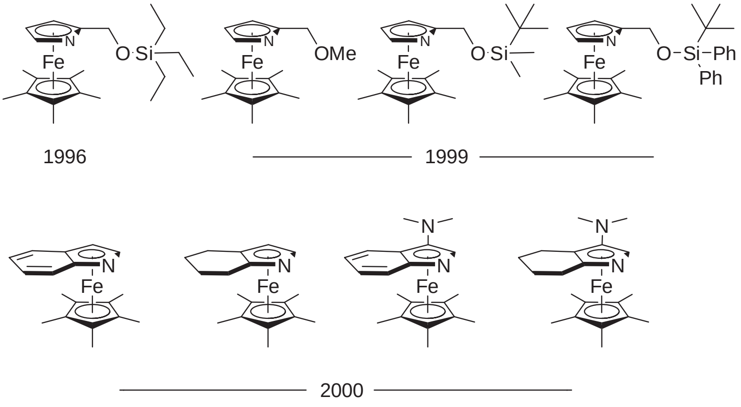
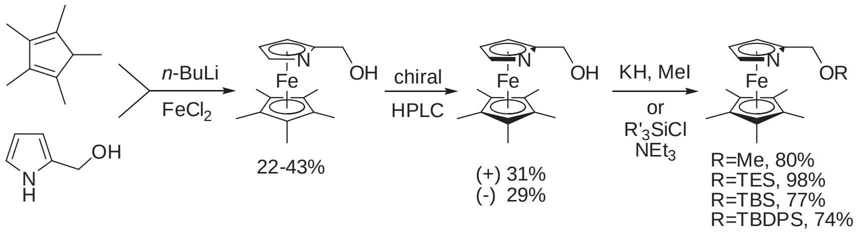
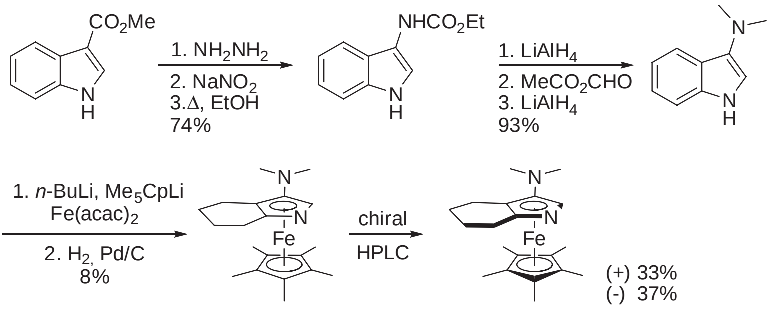


Figure 8.5 Chiral azaferrocene derivatives.



Scheme 8.2

ee [14]. Concerned by the lack of activity of these azaferrocene catalysts, which performed at slower rates than pyridinoferrocenes, Fu's group prepared azaferrocenes with electron-donating substituents (Scheme 8.3). This proved fruitful as the iron dimethylaminotetrahydroindolide complex [15] showed significantly improved Lewis basic properties, allowing for a tenfold decrease in catalyst loadings with respect to TES-hydroxymethylazaferrocene in the addition of alcohol to ketenes. However, the enantioselectivities observed were modest, stressing the need for a more effective chiral environment.



Scheme 8.3

8.2.1.2 **Pyridinoferrocenes**

In a search for chiral DMAP derivatives combining excellent levels of enantioselection with high Lewis basic potential, Fu and coworkers developed more potent and selective catalysts by optimization of the seminal pyridinoferrocene introduced in 1996. Figure 8.6 depicts the different structures prepared. Preparations of all these catalysts make use of pivotal substituted cyclopentenylpyridines (pyrindines). The first-generation synthesis of aminopyrindine compounds consisted of amine functionalization of the pyridine ring of pyrindane followed by desaturation of the indane moiety [11]. Activation of the 4-position of the pyridine by nitration was both low yielding and dangerous considering the explosive propensity of such a product, thereby demanding an alternative preparation protocol [16]; both proce-

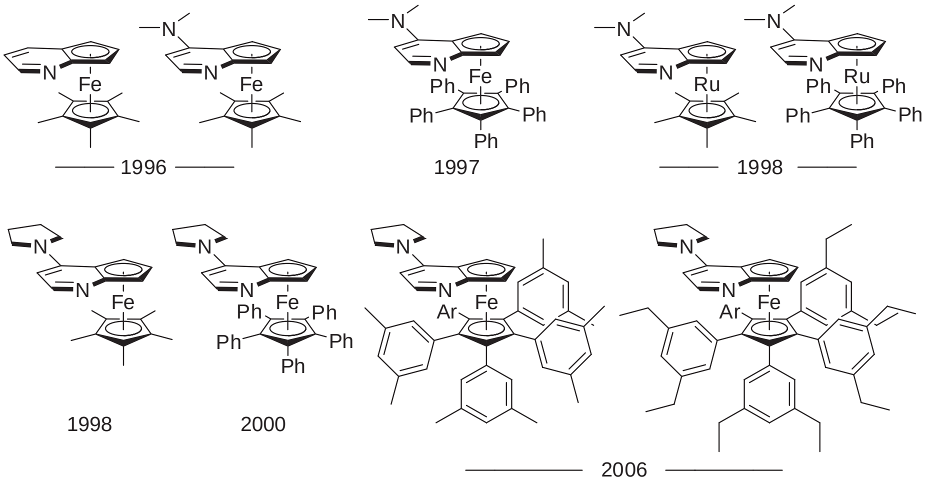
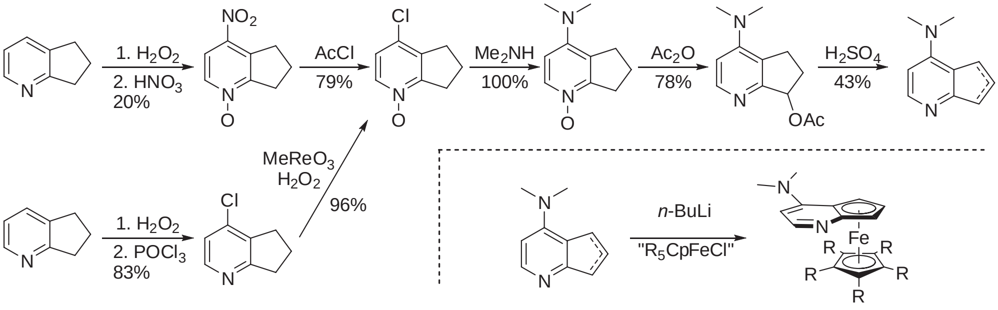


Figure 8.6 Chiral pyridinoferrocene and derivatives.

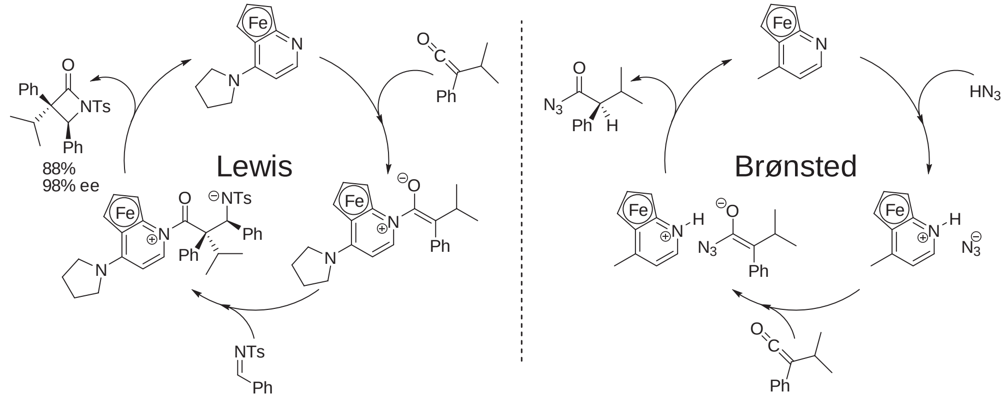
dures are depicted in Scheme 8.4. Final assembly of the ferrocene scaffold requires the formation of the lithium anion of the pyrindine, which is then reacted with a preformed iron complex of the desired pentasubstituted Cp ring. As they are prepared in racemic forms, catalysts must be resolved; in the original procedure this ultimate step was performed using preparative HPLC separation. The second-generation synthesis used a classical crystallization-based resolution with tartaric acid derivatives. This flexible approach thus allows for the examination of substituent effects on the reactivity and on the level of stereocontrol. Hence, steric hindrance at the lower face of the DMAP heterocycle can be modulated by varying the five substituents positioned at the bottom Cp ring of the metallocene. The original pentamethyl-Cp was replaced by pentaphenyl-Cp [17] then by penta(3,5-dimethylphenyl)-Cp and penta(3,5-diethylphenyl)-Cp [18] moieties. Interestingly, in indoline acetylation reactions, the Me_5Cp-based catalyst is almost inactive due to feeble electrophilicity of the derived acylpyridinium ion species, while on



Scheme 8.4

increasing the steric bulk with Ph_5Cp and (3,5-diMePh)Cp the respective promoters lead to more reactive acylpyridinium ions, probably through partial acyl deconjugation from the pyridine ring, and at the same time far better enantioselectivities because of improved facial discrimination. A second parameter that can be tuned is the electron density at the pyridine nitrogen atom, which influences the nucleophilicity of the catalyst and the stability of the derived active intermediate. The reactivity was indeed enhanced when pyrrolidine was put in place of the dimethylamino group, following the observation by Steglich of improved acylating power of pyrrolidinopyridine (PPY) over DMAP. To do so the general protocol was simply modified by replacing dimethylamine with pyrrolidine [19]. Also with the aim of improving reactivity parameters, the influence of the metal center was investigated; DMAP-ruthenocenes were thus prepared and evaluated in comparison with ferrocene derivatives [20]. In fact, substantially faster rates were observed in several transformations; this is attributable to the better cation stabilizing properties of ruthenocenes, together with a less sterically congested environment around the pyridine nitrogen atom, the inter-ring distance being greater in ruthenocene than in ferrocene (3.64 and 3.32 Å, respectively). This last structural feature might also explain the poor results in terms of enantioselection shown by ruthenocene-derived DMAP in most of the transformations studied – the facial differentiation was far less effective than in the iron counterparts.

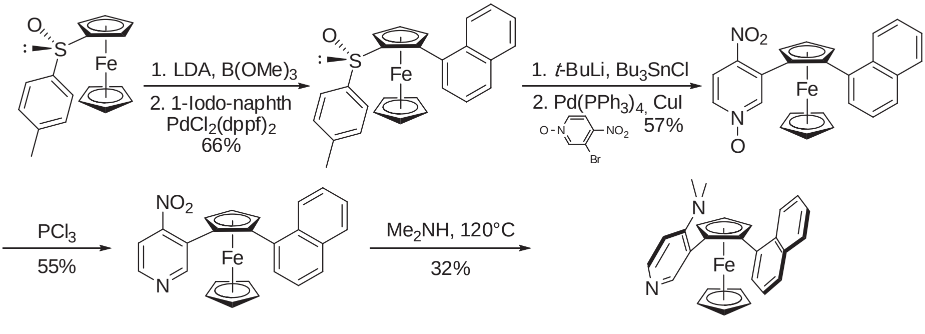
When contemplating the numerous enantioselective transformations that were developed thanks to these catalysts, one cannot regard a specific member of the family as the most selective and the most active. Rather, depending on the reactants involved, some trends can be delineated. Hence, acylation reactions were best performed with encumbered Ph_5Cp-ferrocene catalysts, irrespective of the nature of the acylating agent [21]. In contrast, when ketenes are to be activated, Me_5Cp-ferrocene promoters were preferably employed [22]. Mechanistic investigations performed in reactions involving ketenes also revealed two distinct activation modes depending on the nature of the opposed substrate. These two reaction pathways are exemplified in Scheme 8.5 with a Staudinger



Scheme 8.5

reaction and with hydrazoic acid addition to a ketene. When ketenes are reacted with an electrophile, like an imine, the catalyst acts as a Lewis base, attacking the ketene to form a nucleophilic pyridinium-enolate. This activation mode is thought to operate in ketene formal [2+2] cycloadditions with activated imines,[2] aldehydes, azo, and nitroso compounds, as well as with chlorinating agents. However, when ketenes are presented with an acidic pro-nucleophile, like hydrazoic acid, the pyridine catalyst acts as a Brønsted base, forming an anionic nucleophile paired with the chiral pyridinium ion. Upon addition of the anion to the ketene an achiral enolate is formed that is then enantioselectively protonated by the chiral pyridinium. This alternative behavior takes place with 2-cyanopyrrole, phenols, α-arylaldehydes, and hydrazoic acid [23]. In the latter case 4-methylpyridinoferrocene was employed as catalyst, as its pK_a is more suitable in deprotonation–protonation steps.

Other chiral DMAP catalysts constructed with a metallocene backbone were reported in the literature, the structures and syntheses of which are depicted in Schemes 8.6 and 8.7. In these two cases, strict application of the designation "planar chiral" is arguable, but the ferrocene [24] and cobaltacene [25] catalysts still rely on the facial differentiation brought about by the metallocene to the DMAP plane. Both are 3-substituted derivatives of DMAP and as such are subject to rather great conformational freedom. This could be the origin of the modest enantioselectivities obtained with these catalysts: up to 42% ee in azlactone resolutions with Johannsen's catalyst, and up to 76% ee in Steglich rearrangements promoted by Richard's catalyst. One might imagine that in both structures bottom/up plane differentiation around the DMAP ring is quite strong, while lateral, left/right directions are only moderately differentiated.



Scheme 8.6

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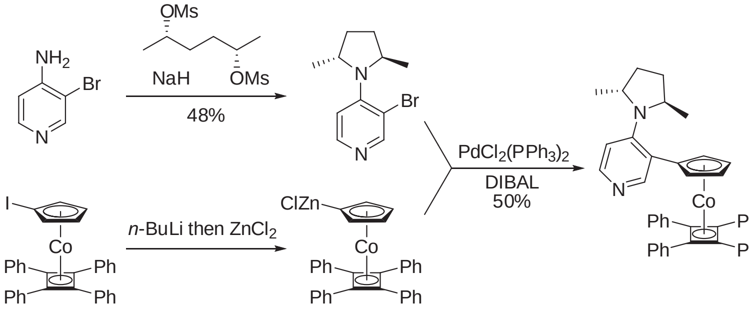
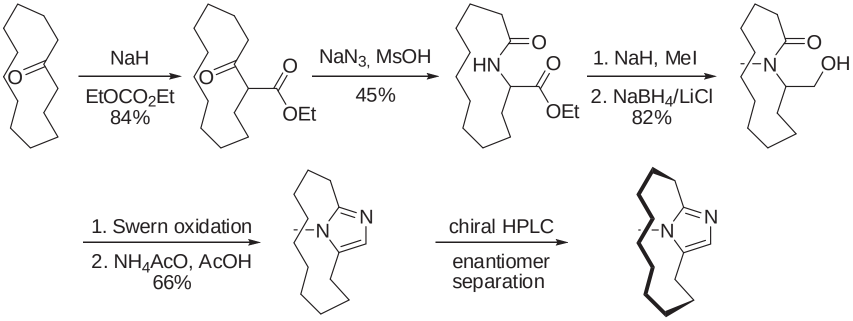
[2] Notably, depending on the relative electrophilicities of the two substrates, ketene and sulfonyl imine, the partner actually activated by the pyridine Lewis base can be either of the two. With poorly activated imines, the ketene partner is attacked to form a pyridinium enolate while with strongly activated imines (*N*-triflylimines), initial attack of the catalyst is envisioned to form a pyridinium-amide species [21c].



Scheme 8.7

8.2.1.3 **Imidazoles**

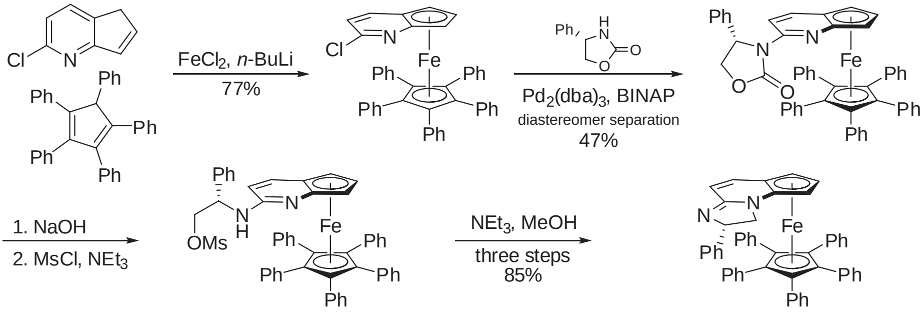
In 2009, Ishida and Saigo [26] explored the possibility of using an imidazole moiety embedded in a cyclophanic structure to promote enantioselective acylation reactions for kinetic resolution of racemic alcohols. Interestingly, this catalyst, the synthesis of which is reproduced in Scheme 8.8, belongs to the “old” family of *ansa*-compounds and not to the paracyclophane series. The *N*-methylimidazole ring is constructed from the ketone of cyclododecanone by β-ketoester formation, Schmidt intracyclic extension to the 13-membered lactam, amide alkylation, and redox adjustment to finally construct the heterocycle with ammonia. Antipodes were eventually separated by preparative chiral HPLC. Importantly, imidazocyclophane proved configurationally stable; heating to 144 °C for 5 h (refluxing xylene) left the chiral compound unaffected. The imidazole base promoted the acylation of phenylethanol in good yield, albeit with feeble enantioenrichment (ester: 32% ee, remaining alcohol: 50%, *s* = 3.1).



Scheme 8.8

8.2.1.4 **PIP: Paracyclophane-2,3-dihydroimidazolo[1,2-*a*]pyridine Bases**

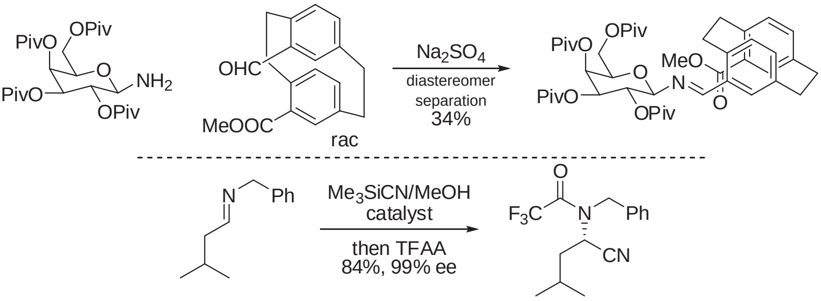
The success of novel chiral architectures embedding an amidine function in enantioselective acylation reactions as reported by the group of Birman [27] fostered the development of ferrocene-based catalysts that merge the excellent reactivity profile of these amidines with the high degree of stereocontrol offered by planar chirality. The groups of Deng and Fossey [28] designed Lewis basic promoters possessing a ferrocene skeleton fitted with an imidazopyridine active moiety. Scheme 8.9 presents the synthesis of the most efficient catalyst.



Scheme 8.9

8.2.1.5 **Imine**

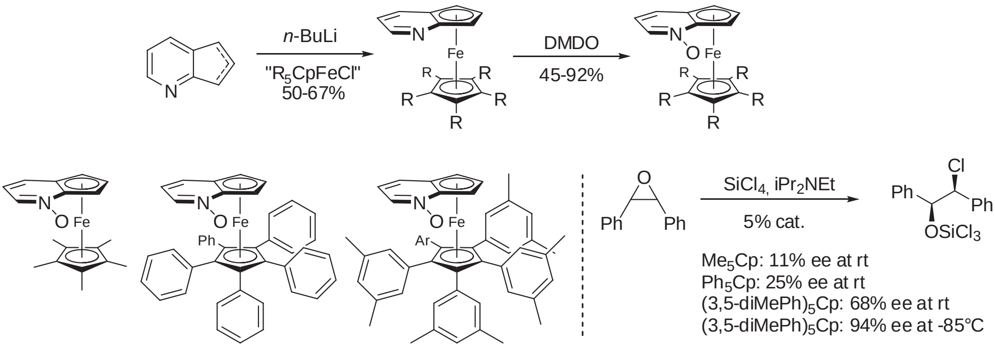
A unique example of a planar chiral catalyst displaying an imine as reactive function was reported by Kunz *et al.* [29] in 2007 (Scheme 8.10). Readily accessible *pseudo-gem* aldehyde-methyl ester Pc [30] in racemic form was condensed with fully protected galacto-pyranosylamine to give diastereoisomeric imines with respect to the Pc chirality. HPLC separation delivered the (*R*p) stereoisomer in pure form, which showed a remarkable ability to perform highly enantioselective Strecker reactions (up to 99% ee). It is assumed that the imine catalyst acts as a Brønsted base toward hydrocyanuric acid produced *in situ* and generates an iminium–cyanide pair that can interact with the imine substrate and direct cyanide addition on a unique face of the latter.



Scheme 8.10

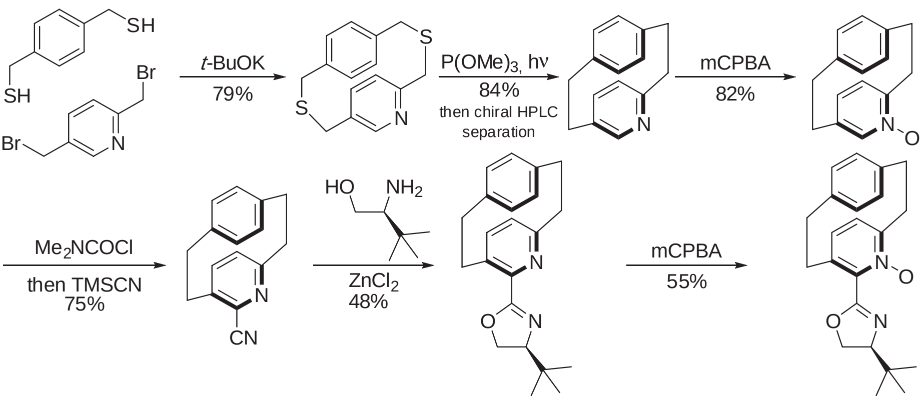
8.2.2
Oxygen Lewis Bases

The first example of a planar chiral catalyst possessing an *N*-oxide as active functionality was reported by Fu *et al.* [31] in 2001. Scheme 8.11 presents the two-step general methodology for preparing pyridinoferrocene *N*-oxides, the structures of three members of this family of promoter, and the studied reaction, namely, the Lewis base mediated *meso*-epoxide ring opening by tetrachlorosilane. A very interesting conclusion of this study is the shielding role played by the bottom pentasubstituted Cp ring to ensure optimal stereocontrol. Compared to previously presented pyridinoferrocene catalysts, the active center is farther from the chiral surrounding created by the metallocene moiety. Thus, to restore a facial differentiating environment around the oxygen atom, larger appending substituents were required. Hence upon a gradual increase of the bulkiness at the ferrocene lower ring, ee values progressively increased.

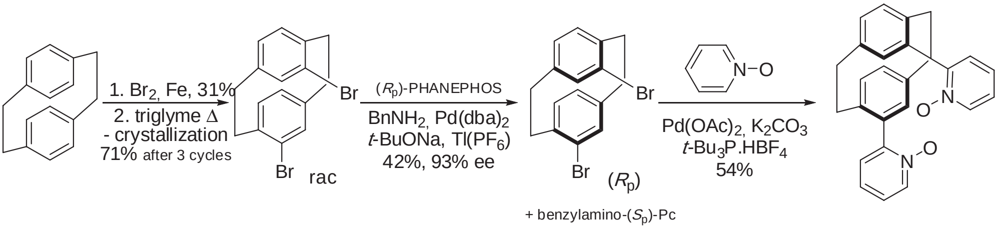


Scheme 8.11

The problem associated with the remoteness of the oxygen atom from the planar chiral environment can be addressed by placing the pyridine *N*-oxide group within a cyclophanic structure. This idea was brought to practice by the group of Andrus [32] in 2006. They reported the preparation of a pyridinophane molecule bearing an extra stereogenic center (Scheme 8.12). This, incidentally, perfectly exemplifies the classical synthetic route to paracyclophanes relying on the photochemical extrusion of sulfur from a bis-sulfide macrocycle in the presence of a thiophilic phosphite. The use of this compound as Lewis base activator allowed the enantioselective addition of allyltrichlorosilane onto anisaldehyde in 91% yield and 90% ee, as the best result. Recently, opportunities offered by a bis-*N*-oxide functionalized paracyclophane core were investigated by the group of Rowlands [33]. This synthesis relies on the availability of (S_p)-*pseudo-ortho* dibromo-Pc [34] and, therefore, perfectly illustrates the specificities of the chemistry of chiral Pc derivatives (Scheme 8.13). Dibromination of Pc gives a mixture of regioisomers in which the *pseudo-para* is the most abundant; however, the *pseudo-ortho* isomer is readily separated by simple crystallization. Mother liquors are thermally equilibrated in reflux-



Scheme 8.12



Scheme 8.13

ing triglyme and another crop of the desired isomer is then crystallized. After three cycles, a 71% yield of *pseudo-ortho* dibromo-Pc is obtained in racemic form. Kinetic resolution via palladium-catalyzed amination was used to access to the sole (R_p) enantiomer. Diphosphine ligand (R_p)-Phanephos, itself derived from dibromo-Pc, allows preferential benzylamination of the (S_p)-dibromo-Pc enantiomer, leaving the (R_p) isomer unreacted. From this chiral starting material, palladium mediated cross-coupling with pyridine *N*-oxide affords the difunctional catalyst. This bis-Lewis base performed modestly in allyltrichlorosilane addition onto benzaldehyde: 72% yield with 38% ee in the best case. Activation of chlorotrimethylsilane was also attempted using a ferrocene-derived azaphosphinine fitted with a nucleophilic aldehyde moiety [35]. The feeble selectivities obtained can be ascribed to the lack of a properly differentiating environment around the active oxygen atom.

8.2.3
Phosphine

Planar chiral phosphines were used as ligands for transition metals as early as 1974 [36], but a 30 year period of latency elapsed before their first use as organocatalysts [37]. Figure 8.7 presents the phosphines with planar chirality used as

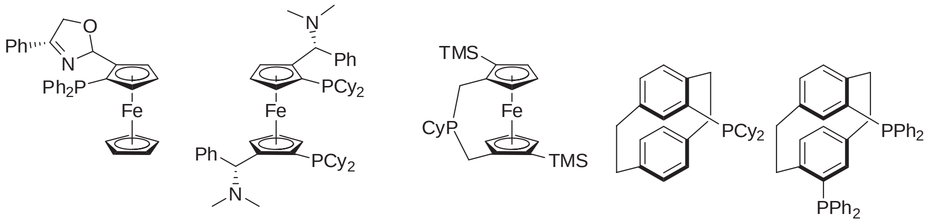
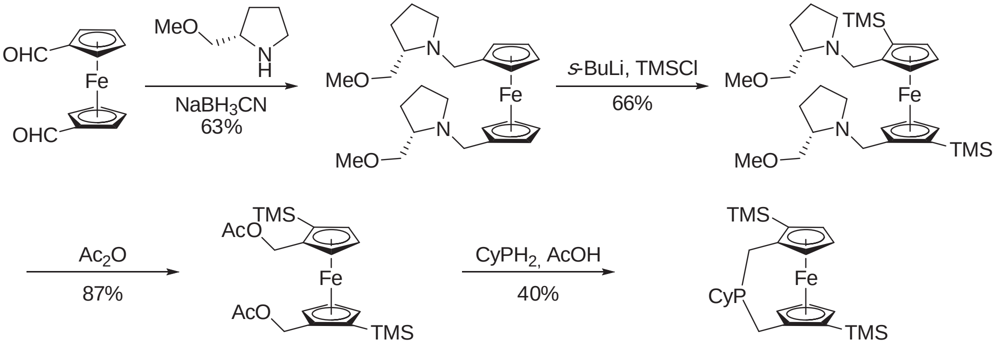


Figure 8.7 Some phosphines with planar chirality.

Lewis bases for the activation of Michael acceptors. Early contributions reported the catalytic abilities of ferrocene-based phosphines in asymmetric aza-Baylis–Hillman [38] and Morita–Baylis–Hillman (MBH) [39] reactions; however, enantioselectivities were below 70% ee and were largely surpassed by Binap derivatives. Paracyclophanic monophosphines were studied as promoters in allylic substitutions [40] on MBH adducts, again affording moderate selectivities, with the dicyclohexyl-derivative exhibiting the best levels at 66% ee, with 68% conversion. The related *pseudo-ortho* diphosphino-Pc "Phanephos" was tested in Lewis base activation of allenoates [41], but was outranked by binaphthyl-phosphepine catalysts. All these catalysts were actually known compounds, prepared previously for their complexing properties and reused as organocatalysts. In 2008 the group of Marinetti [42] reported their successful development of planar chiral *ansa*-phosphinoferrocenes specifically designed for organocatalysis purposes. The diastereoselective synthesis is reported in Scheme 8.14; it benefits from the long-standing methodology for preparing planar chiral disubstituted ferrocene compounds. It relies on the stereo-directed *ortho*-lithiation protocol of ferrocenes monosubstituted with a chiral methoxymethyl-pyrrolidine moiety, here elegantly used in a twofold manner. After introduction of two TMS groups, the directing arms are converted into hydroxymethyl esters, ready to undergo a double S_N1 reaction with cyclohexylphosphine in an inter-deck fashion to give the *ansa*-ferrocene catalyst. This remarkable structure features a strongly differentiated left/



Scheme 8.14

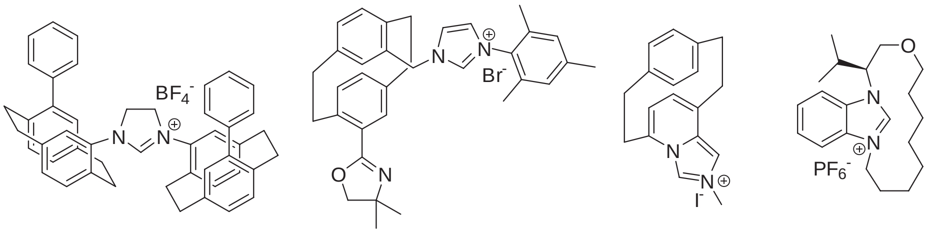
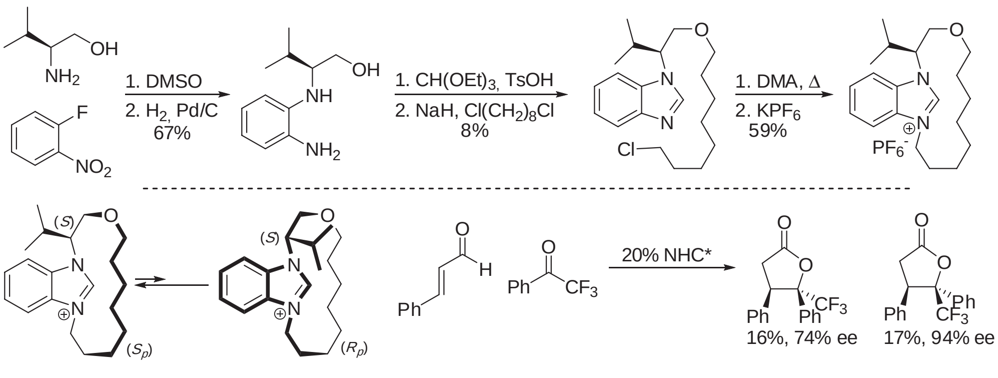


Figure 8.8 Structures of some imidazolium salts used as carbene precursors.

right environment with respect to the phosphorus lone-pair, with the C_2 symmetry axis eliminating any need for additional symmetry breaking toward facial discrimination. Additionally, maximum phosphine nucleophilicity is assured thanks to the strong electron-donating property of the cyclopentadienyl group.

8.2.4
N-Heterocyclic Carbenes

Planar chiral imidazolium salts are scarcely found in the literature and only a single report details their use as promoter in organocatalysis. Figure 8.8 gathers together the molecular structures of imidazolium salts described by Andrus [43], Bolm [44], and Fürstner [45] used as carbene precursors for transition metal complexation. The benzimidazolium salt on the right-hand hand, by Ishida and Saigo [46], was used in benzoin-type cross condensation and thus represents to our knowledge the only example of a planar chiral N-heterocyclic carbene (NHC) used in organocatalysis. This compound is prepared from valinol in six steps and displays interesting configurational behavior. The tethered chain is long enough to allow facile inversion between (S_p) and (R_p) configurations through rope-skipping, even at low temperatures. However, the presence of a chirality center renders these conformations diastereomeric: (S,S_p) and (S,R_p) and induces a great preference for one conformer in the equilibrium depicted in Scheme 8.15. It was, moreover,



Scheme 8.15

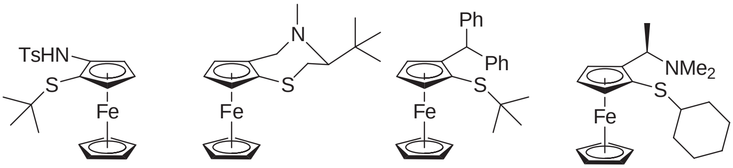
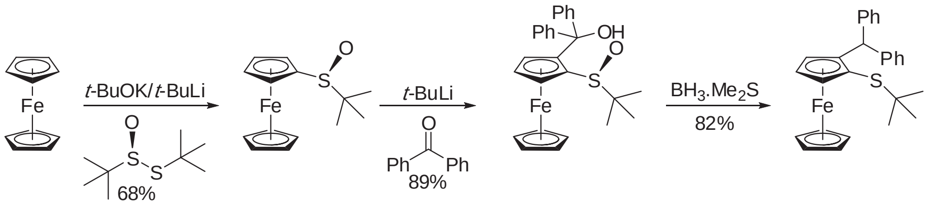


Figure 8.9 Examples of sulfonium ylide precursors.

shown that diastereomeric carbenes were kinetically dissimilar, with the major isomer (S,S_p) being the most reactive, with a shielding effect from the isopropyl group drastically decreasing the nucleophilicity of the minor (S,R_p) diastereomer. This induced good enantioselectivities in the cross-annulation products between cinnamaldehyde and an activated ketone.

8.2.5
Sulfides

The group of Metzner [47] investigated ferrocene derivatives incorporating a thioether group as catalysts for asymmetric epoxidation reaction of aldehydes with benzyl bromide. Figure 8.9 shows some examples of sulfonium ylide precursors, some of which rely both on centered and planar chiralities, others only on planar stereogenicity. To showcase typical synthetic work carried out on the preparation of enantiopure ferrocenyl sulfides, Scheme 8.16 presents a stereoselective sequence exploiting a sulfoxide directed ortho-lithiation strategy. Epoxides were obtained with a maximum level of enantioselection of 68% with the left-hand catalyst. The authors clearly observed a balance between reactivity and selectivity in these systems. The epoxidation process involves initial sulfide attack on benzyl bromide, and with two lone pairs the sulfur atom can lead to two diastereomeric sulfonium ions, which slashes the chances of high selectivity from the start. To preclude such unselective addition, the catalyst structure has to integrate a shielding moiety close to one of the sulfur lone pairs, consequently dividing the addition rates by a factor two. Even then, the subsequent ylide attack onto the carbonyl group requires strong facial differentiation around the sulfur reactive center to properly orientate the ylide carbon atom. Hence, only catalysts that also incorporate a bulky substituent in the vicinity of the most accessible lone pair showed relevant levels of selectivity. In summary, studied promoters are either selective but with very poor reactivity or pleasingly active but unselective.



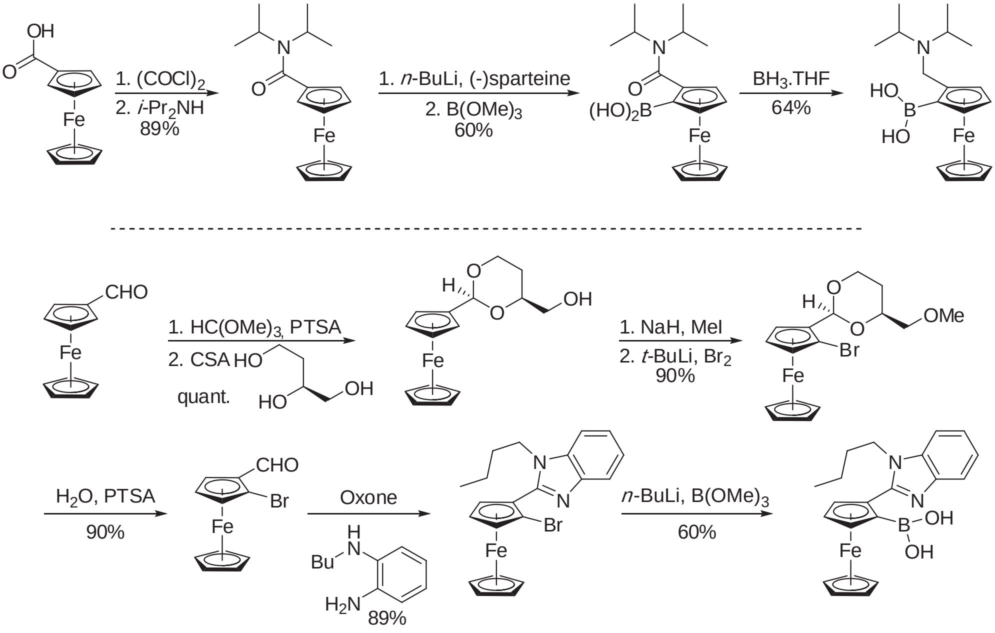
Scheme 8.16

8.3
Lewis/Brønsted Acids

Here we consider the activation of substrates via enhancement of their electrophilicity by catalytic species able to interact with their HOMO orbitals. Such a catalyst can be a Lewis acid [48] interacting via a vacant orbital, or alternatively it can operate via a polarized hydrogen atom, thus belonging to the continuum between a Brønsted acid [49] and a H-bond donor [50]. In fact, planar chiral catalysts belonging to these categories are extremely scarce. In the first category, only one report is found, about a ferrocenyl-boronic acid, while in the second category only three contributions, involving phenols and thioureas as H-bonding functions, can be found. Quite surprisingly no studies were directed toward the design and use of an acidic group – phosphoric acid, bisulfonamides, or others – within a planar chiral framework.

8.3.1
Boronic Acids

Although boron is a metalloid, one can nonetheless include boron-derived compounds in a book on organocatalysis as not being transition metal containing catalysts! Planar chiral boronic acids have been employed as amide coupling catalysts, actually as bifunctional Lewis acid/base activators. Whiting's [51] group reported the preparation [52] of two amino-boronic ferrocenes (see Scheme 8.17). Their use

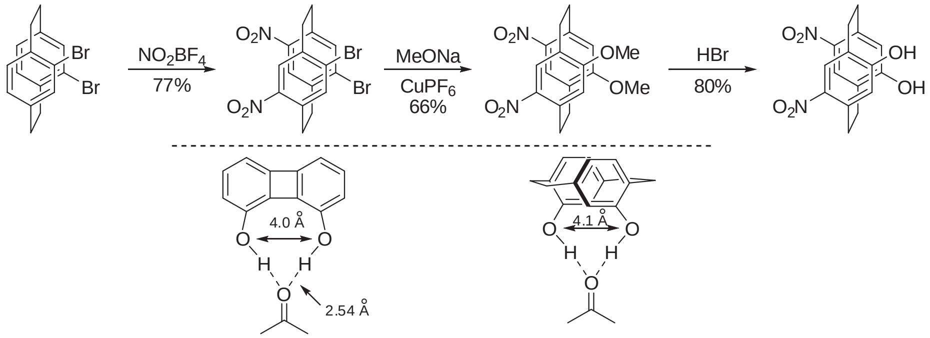


Scheme 8.17

in coupling between benzoic acid and racemic phenylethylamine under kinetic resolution conditions gave the corresponding amide in 21% yield and 41% ee.

8.3.2
Phenols

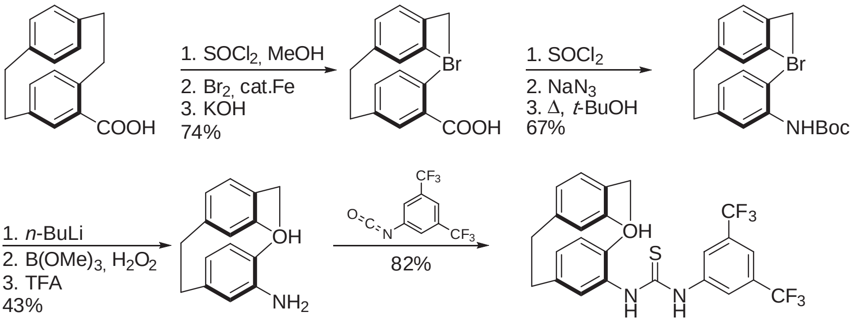
The role of phenols as accelerators in cycloaddition reactions was recognized as early as 1942 by Wassermann [53]. More than four decades later, Hine reported crystallographic evidence of strong interactions between a particular bisphenol and a carbonyl group. This opened the way to electrophilic activation of oxygenated reactants by twofold interaction between two lone pairs of an oxygen atom and two phenol moieties properly arranged in space. The group of Braddock [54] employed this ability of bisphenols to enhance the electrophilicity of the complexed partner to trigger various reactions, like Diels–Alder cycloaddition with acroleins or nucleophilic ring opening of epoxides. For this purpose they exploited the Pc backbone, where *pseudo-ortho* hydroxyl groups cannot realize intramolecular H-bonding but are optimally positioned to give rise to double H-bonding with an additional oxygenated moiety. It was also shown that the introduction of nitro groups, which lowers the pK_a of the phenols, could be beneficial to catalytic activity by strengthening the H-bond donor ability; see Scheme 8.18 for the synthesis of the corresponding phanol. Despite investigations involving more substituted derivatives, phanol-based catalysts proceeded without any detectable enantioselection in the studied reactions.



Scheme 8.18

8.3.3
Thioureas

More recently, Paradies [55] and coworkers developed activators that also rely on the double H-bonding properties of urea derivatives. The most selective catalyst actually had a third H-bonding moiety. Scheme 8.19 depicts the preparation of this *pseudo-gem* thiourea-phenol compound. It promoted nitrostyrene reductions



Scheme 8.19

by Hantzsch esters with modest selectivities (24% ee in the most favorable case), which is attributed to the lack of conformational preorganization.

8.4
Redox Reactions

8.4.1
Flavin Derivatives

To close this chapter on planar chiral organocatalysts, we examine flavin derivatives, which constitute an historical example of a planar chiral compound used as promoter in an enantioselective transformation without the aid of a transition metal (Figure 8.10). In 1988, Shinkai *et al.* [6] reported the asymmetric oxidation of sulfides into sulfoxides by hydrogen peroxide in the presence of flavinophane, observing ee's as high as 65%. More recently, Cibulka *et al.* [56] described a simpler flavin compound exhibiting a similar degree of stereocontrol in sulfide monooxidation. The same concept was adapted by Imada and Murahashi [57] to the Bayer–Villiger reaction of cyclobutanones using C_2-symmetrical bis-flavin catalyst with ee's up to 74%. The latter was, interestingly, prepared diastereoselectively using chiral induction brought about by two stereogenic centers present within the interplanar tether.

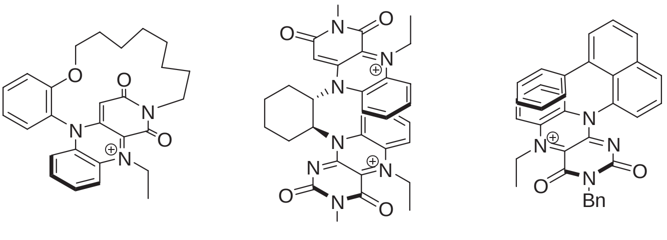
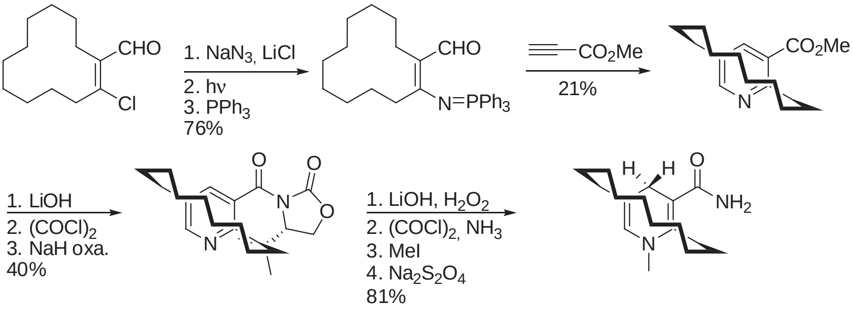


Figure 8.10 Flavin derivatives used as promoter in enantioselective transformations without the aid of a transition metal.

8.4.2
Hantzsch Esters

So far, no example of reduction has been reported in the literature using a catalytic system relying on planar chirality. However, *ansa*-derivatives of Hantzsch esters were developed by Kanomata and Nagata [58] as NADH model compounds (Scheme 8.20). These reagents displayed excellent hydrogen transfer abilities – reduction of carbonyl compounds was achieved with almost perfect enantioselectivity. There is no doubt that, coupled with a proper metal-based hydride-transfer system, such NADH models could perform well in a catalytic version.



Scheme 8.20

8.5
Summary and Conclusions

The structural features of planar-chiral compounds make them interesting platforms for the creation of a strongly differentiated chiral environment around a reactive center. Face-to-face arrangement must, however, be properly exploited if a good compromise between reactivity and selectivity is to be found. Fu's ferrocenyl-DMAP represents the optimal combination where nearly perfect facial discrimination is possible together with very high catalytic activity thanks to its electron-rich nature. Paracyclophane-based promoters still have to achieve such a fundamental breakthrough. Interesting results can be expected following the path opened up by Paradies and Rowlands with disubstituted Pc derivatives and bifunctional activation settings. This would be greatly facilitated if more efficient stereoselective routes could be found to prepare enantiopure Pc compounds [59].

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2 IUPAC definition of *planar chirality*: Term used by some authorities to refer to stereoisomerism resulting from the arrangement of out-of-plane groups with respect to a plane (chirality plane). It is exemplified by the atropisomerism of (*E*)-cyclooctene (chiral plane = double bond and attached atoms) or monosubstituted paracyclophane (chiral plane = substituted ring). The configuration of molecular entities possessing planar chirality is specified by the stereodescriptors *R*p and *S*p (or *P* and *M*). The definition is given in Moss, G.P. (1996) Basic terminology of stereochemistry. *Pure Appl. Chem.*, **68**, 2193–2222.

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9

Dynamic Approaches towards Catalyst Discovery

Patrizia Galzerano, Giulio Gasparini, Marta Dal Molin, and Leonard J. Prins

9.1

Introduction

Nature is a prodigious source of inspiration for scientists, and the development of catalysts able to mimic enzymes both in terms of activity and selectivity is one of the main challenges for chemists [1, 2]. Catalyst discovery is the finding of efficient man-made systems that can convert often valuable substrates into the desired products with high levels of regio- and stereoselectivity. This is a very challenging task as it requires the identification of molecules able to stabilize elusive and transient transition structures that are formed along the reaction coordinate. To this end two possible approaches can be discerned for catalyst discovery: either through rational design or through a combinatorial approach relying on the high-throughput synthesis and screening of potential catalysts [3, 4]. Although the rational design approach benefits strongly from computational techniques, it remains a very daunting task to predict the combined effect of simultaneous covalent and non-covalent interactions between the catalyst and the transition state. For that reason, there is a strong current interest in catalyst development that uses innovative combinatorial approaches [5–7]. This permits a systematic investigation of the chemical space, allowing the simultaneous evaluation of a large number of substrates within a short time period. Here, the difficulty relies on the possibility of synthesizing catalyst libraries as large as possible in terms of size and, more importantly, structural diversity. Evidently, the search for catalysts through this approach is advantageous if the catalytic systems are formed by easily synthetically accessible and adaptable subunits. In this context, the use of dynamic chemistry, that is, chemistry relying on reversible bond formation (covalent [8], non-covalent [9], or a combination [10]), presents several advantages and offers great potentiality in the field of catalyst discovery (Figure 9.1). This chapter illustrates the application of dynamic chemistry for the discovery of organocatalysts, in particular related to two concepts that are inherent to reversible bond formation: self-assembly and self-selection. Self-assembly relates to the spontaneous formation of well-defined complex structures upon mixing small subunits equipped with complementary recognition units. It will be shown that self-assembly is attractive for the rapid

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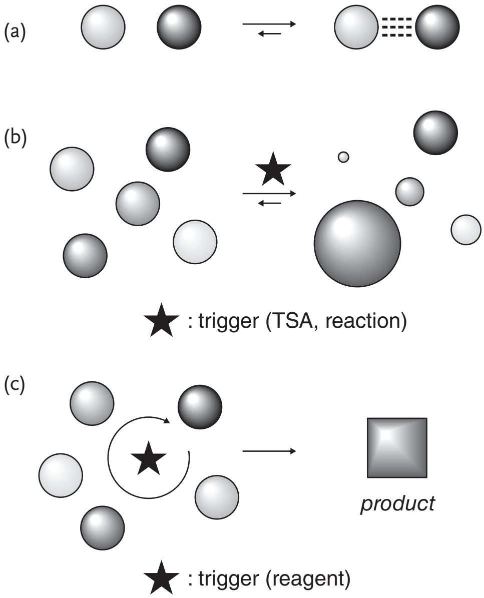


Figure 9.1 Schematic representations of (a) self-assembled, (b) self-selected, and (c) self-evolving catalysts. Reproduced with permission from Reference [7]. Copyright 2010 (Wiley-VCH).

preparation of combinatorial libraries of organocatalysts. In addition, self-assembly provides for easy access to cage-like molecular structures that can encapsulate reagents, with consequences for the chemical transformation. Self-selection relies on the spontaneous selection of complementary components by a target. It will be shown that the use of a transition state analog as target results in the straightforward identification of functional groups able to assist in catalysis. Finally, it will be shown that a dynamic mixture of reagents can auto-converge to a single product through a combination of molecular Darwinian evolution and autocatalytic pathways.

9.2
Self-Assembly

The superb interplay between functional groups in the active site of enzymes, the substrate, *and* the transition state has led chemists to propose artificial systems able to mimic (at least part of) these recognition events [11, 12]. Such supramolecular systems have served as model systems to explain phenomena observed in enzymes and have permitted very detailed studies that have contributed to a mechanistic understanding of the reaction pathways involved. Although occasionally catalytic efficiencies have also been obtained that come close to the values of the natural counterparts, as a general rule the artificial systems do not live up to expectations and industrial applications are rare [13]. Over quite recent years the field of supramolecular catalysis has been revitalized by input from chemists working with transition metal based catalysts [14, 15]. Rather than by enzymes, the design of these supramolecular catalysts is inspired by "classical" organometallic catalysts. Here, the scope is to alter or fine-tune the properties of known organometallic catalysts via the creation of supramolecular constructs. The intrinsic advantage compared to *de novo* enzyme development is evident: one starts with a catalytic core unit, which ensures a basic reactivity or selectivity. Several elegant examples have been reported showing the supramolecular approach for the fine-tuning of transition metal complexes – via non-covalent interactions with small coordinated ligands [14, 15]. Here, we will show that such a supramolecular approach is also highly attractive for the modulation of organocatalysts. In particular, examples will be discussed in which specific recognition modules are introduced in the ligands with the specific aim of creating organocatalyst libraries. Closely related catalytic systems relying on electrostatic interactions (e.g., asymmetric counteranion-directed catalysis) are extensively discussed elsewhere in this volume.

9.2.1
Self-Assembled Organocatalysts

A key strategy for the development of supramolecular catalyst libraries is the use of particular recognition motifs that cause the spontaneous formation of the active catalyst. The attractive feature is that a large number of catalysts can then be simply prepared by mixing a reduced number of subunits. An early example was reported by the group of Aida and Konishi in which a catalytic active site for the ring-opening reaction of glycidyl methyl ether **1** with 4-*tert*-butylthiophenol **2** is built through the hydrogen-bond induced dimerization of 2-ureidoisocytosine derivative **4** (Figure 9.2) [16]. Starting from the well-known notion that the presence of both

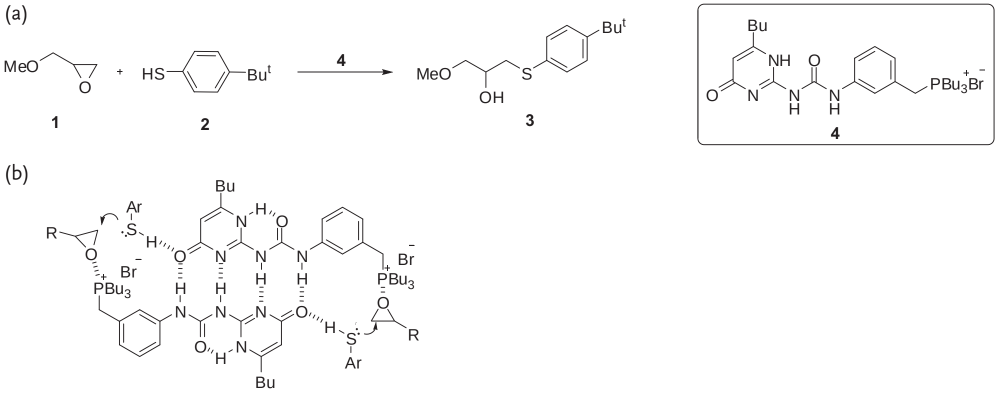


Figure 9.2 (a) Ring-opening reaction of **1** by **2** in the presence of catalyst **4**; (b) proposed structure of the catalytically active complex.

an acid functionality (for the activation of epoxide **1**) and a base (for facilitating the nucleophilic attack by thiol **2**) can accelerate the reaction, catalyst subunit **4** was designed. The selected H-bonding motif based on 2-ureidoisocytosine causes spontaneous head-to-tail dimerization in $CDCl_3$ through quadruple H-bond formation [17]. Dimerization results in a well-defined spatial arrangement of the phosphonium salt (weak Lewis acid) and the basic oxygen atom of the C(4)=O (weak Lewis base), permitting cooperative acid/base catalysis. The proposed mechanism was confirmed by the observation that a non-functionalized analog of **4** showed a lower activity. Moreover, the authors have shown that the orientation of the phosphonium group and the steric bulk around the C(4) carboxylic moiety are both important for good catalytic activity. Furthermore, the very low rate enhancement observed in the presence of an *N*-methylated derivative of **4**, which is unable to form a hydrogen-bonded dimer, gave further support for the proposed cooperative catalysis.

Complementary hydrogen-bonding interactions have also been used by the group of Clarke [18, 19] for the construction of catalyst libraries based on the self-assembly of chiral proline-derived pre-catalyst **8** [designated (*S*)-ProNap] with a series of achiral substrates (Figure 9.3). These studies were aimed at modulating the stereoselectivity of the asymmetric nitro-Michael reaction of ketones and nitrostyrenes simply by modifying the achiral co-catalyst. Since catalyst formation relies on self-assembly, this provides easy access to a catalyst library with different

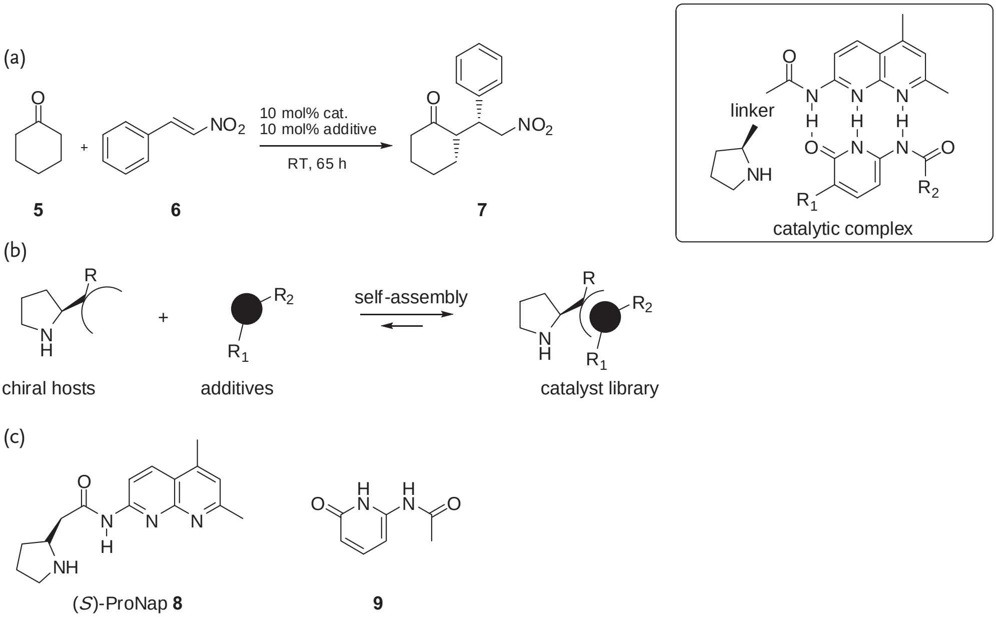


Figure 9.3 (a) Asymmetric nitro-Michael reaction of ketones and nitrostyrenes catalyzed by self-assembled complexes (b); (c) best performing pre-catalytic unit **8** and achiral additive **9**.

steric environments around the chiral catalytic center. Interestingly, the two-component catalytic system was in all cases more efficient than (*S*)-ProNap itself and all the combinations gave better results in terms of stereo-control, thus enhancing the diastereo- and enantioselectivity of the reaction. For example, (*S*)-ProNap alone gave the product in 70% yield with a 41 : 1 ratio of diastereoisomers, but with very low ee (7%). However, in the presence of 1 equiv. (relative to the catalyst) of achiral additive **9** the yield increased to 98% with a diastereomeric ratio of 59 : 1. Impressively, the ee jumped up to 72% under the same conditions. Moreover, it was found that also the absolute configuration of the constructed stereogenic center is to some extent influenced by the presence of the complementary additives, allowing in principle a programmable access to both enantiomers.

A similar approach aimed at delivering new organocatalysts by means of the designed modular assembly of two distinct catalytic moieties has been illustrated recently by Mandal and Zhao [20]. In this example, the catalytic system is built up through electrostatic interactions between the carboxylic acid of proline (or a different α-amino acid) and a tertiary amino group of a second unit carrying a thiourea moiety as stereocontrolling element (Figure 9.4). The expected acid–base

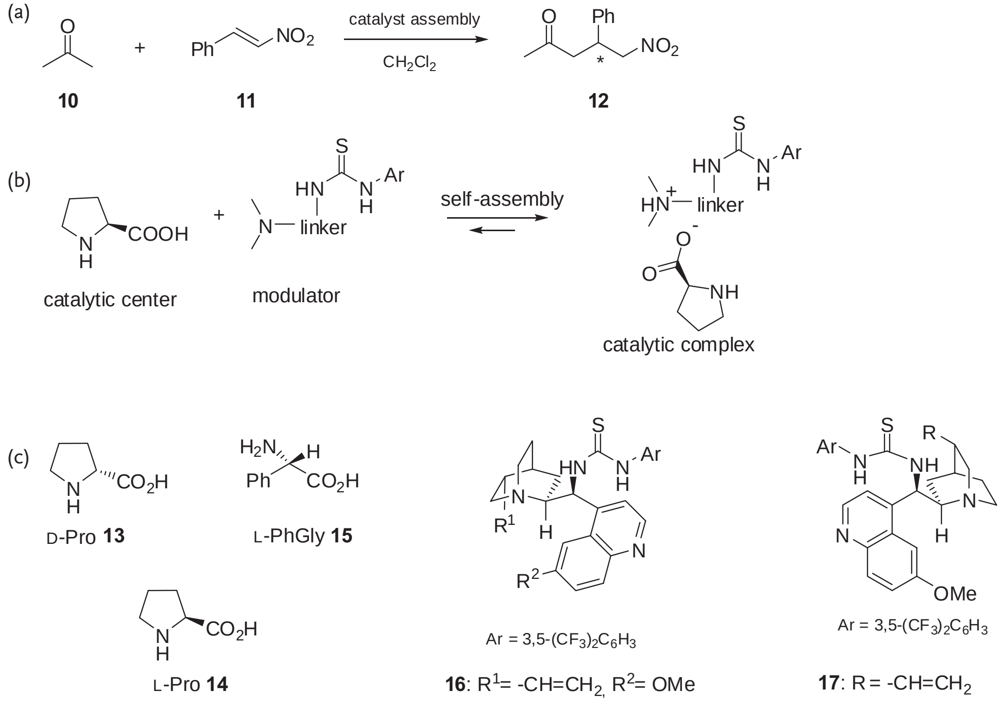


Figure 9.4 (a) Asymmetric nitro-Michael addition of ketones to nitrostyrenes catalyzed by catalytic complexes obtained through self-assembly (b); (c) examples of catalytic and modulating units.

reaction leads to the formation of a chiral self-assembled ammonium salt. In this way, a library of several structurally diverse entities was created by preparing different combinations of α-amino acids and alkaloid derivatives and tested as catalysts in the asymmetric nitro-Michael addition of ketones to nitrostyrenes. In some cases this leads to excellent results in terms of catalytic efficiency and enantioselectivity. In particular, strong matching and mismatching effects were observed with thiourea derivative **16**. No conversion of *trans*-ß-nitrostyrene was detected after 72 h when L-proline **14** was used. Remarkably, the use of D-proline **13** gave the product in 88% yield after just 20 h, with an ee of 66%. The use of either **16** (0%) or D-Pro **13** (<5%) alone gave poor conversions.

The validity of this approach was further demonstrated by the poor enantioselectivities obtained for proline-based catalytic centers that are unable to self-assemble with alkaloids, demonstrating that enantioselectivity is indeed due to the two-component supramolecular complex. As stated by the authors, these results indicate that this catalytic system is different from the reported asymmetric counteranion-directed catalysis (ACDC) [21] since in that case the stereocontrol is achieved mainly through steric effects instead of hydrogen bonding.

Further screening studies identified L-phenylglycine **15** and quinidine **17** as a promising catalytic complex, yielding the Michael adduct derived from acetone in its (*R*)-configuration in 95% ee. This catalyst was also highly efficient in the addition of longer-chain ketone substrates, affording the Michael products with excellent enantioselectivities and good *syn*- diastereoselectivities in almost all cases. Interestingly, the catalysts obtained through self-assembly of L-phenylglycine **15** or L-proline **14** with **17** gave opposite absolute and relative configurations of the forged stereogenic centers, as rationalized by the authors with the transition states depicted in Figure 9.5.

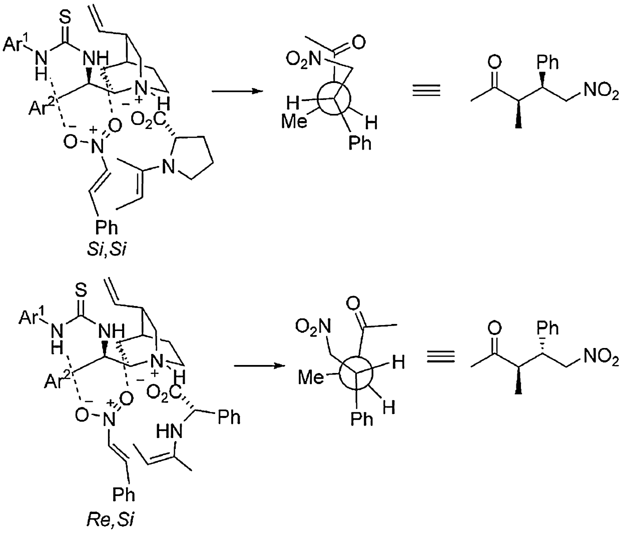
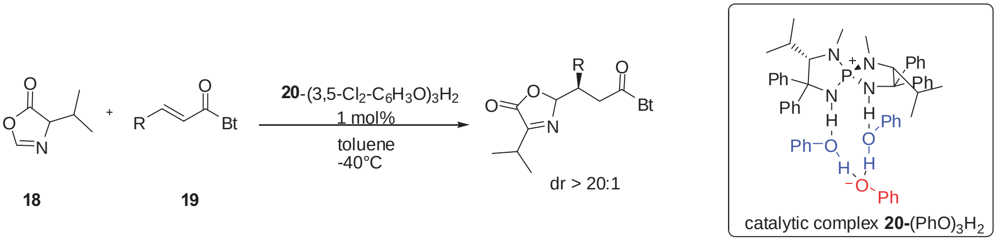


Figure 9.5 Proposed transition-state structures.

A final example of a functional supramolecular catalytic system obtained through self-assembly was recently reported by Ooi and coworkers [22]. The proposed catalyst (**20**) is based on the self-assembly of a chiral aminophosphonium ion, two phenols, and a phenoxide anion into a structured architecture held together by a network of hydrogen bonds (Scheme 9.1). Catalytic studies revealed that all components were essential for catalytic activity, highlighting the possibility of modulating the stereoselectivity of the reaction by modification of either the achiral or chiral components of the supramolecular construct. The catalytic system was highly efficient in promoting the addition of acyl enolates to α,β-unsaturated acylbenzotriazoles with almost perfect enantioselectivities. The mechanism proposed by the authors involves exchange between the phenolate and the enolate derivative in the organized chiral space with a subsequent reaction as nucleophile towards the α,β-unsaturated esters. Another important peculiarity of the presented model is that the stereochemical information is transmitted from the phosphonium ion to the enolate through the achiral phenol molecules, thus extending the chiral environment to the whole supramolecular architecture.

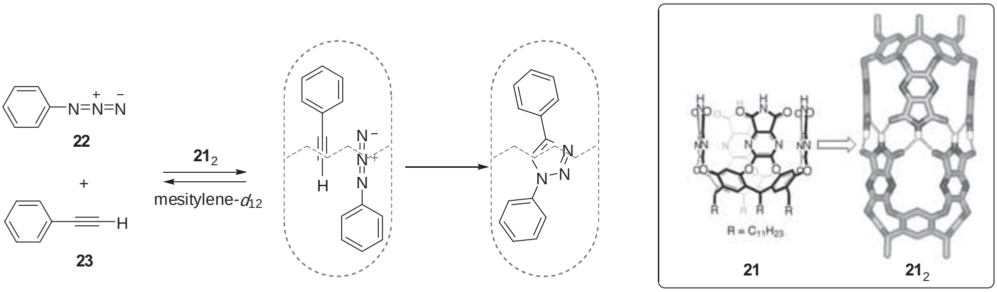

18
19
20-(3,5-Cl$_2$-C$_6$H$_3$O)$_3$H$_2$
1 mol%
toluene
-40°C
dr > 20:1
catalytic complex 20-(PhO)$_3$H$_2$

Scheme 9.1 Addition of acyl enolates to α,β-unsaturated acylbenzotriazoles.

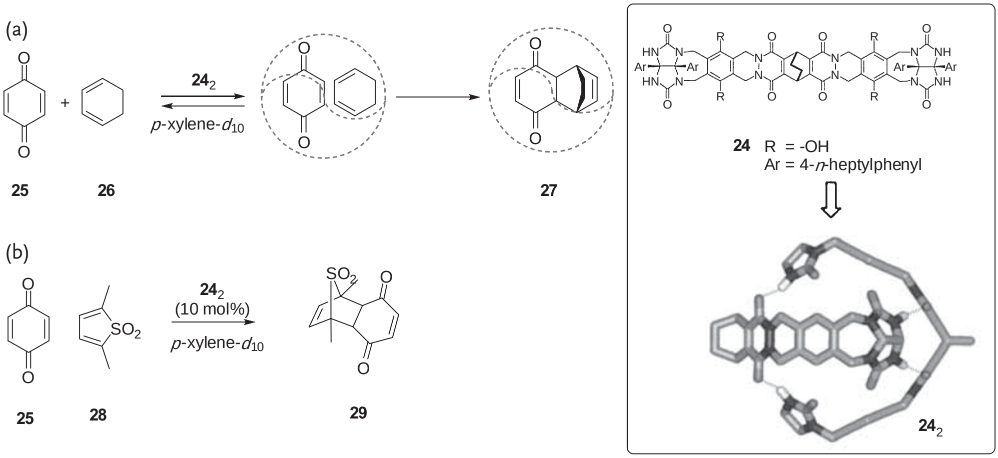
9.2.2
Catalysis in Confined Self-Assembled Space

The active site of an enzyme plays a crucial role in “removing” reactants and transition states from the bulk solvent and placing them in a local chemical environment that is optimized for the chemical reaction. In addition, the confinement of two (or more) reactants in the active site causes a strong increase in effective molarity with a concomitant increase in rate. Recent developments in the field of supramolecular catalysis are devoted to reproducing these effects in synthetic systems [23]. In fact, the idea of controlling the reaction location by creating a well-defined three-dimensional structure in which the substrates can be “encapsulated” (through covalent or non-covalent interactions) can provide new tools for the development of catalysts. Self-assembled capsules are formed by two or more subunits that in solution are able to self-associate into a supramolecular structure by means of multiple non-covalent bonds, such as hydrogen bonds, ionic, and metal–ligand interactions [24].

Major contributions in the field of hydrogen bond-based capsules have been provided by Rebek and colleagues, developing among others the cylinder-shape capsule $\mathbf{21}_2$ and the "softball" capsule $\mathbf{24}_2$ (Schemes 9.2 and 9.3) [25]. The 1,3-dipolar cycloaddition reaction of phenyl azide (**22**) and phenylacetylene (**23**) was investigated in the presence of $\mathbf{21}_2$, a cylindrical capsule formed upon the dimerization of two vase-shaped cavitands driven by the formation of a network of hydrogen bonds between the imide functionalities [26]. This nanoreactor can accommodate simultaneously two aromatic substrates, which are forced into an edge-to-edge orientation and a consequent contact of their peripheral substituents (Scheme 9.2). Interestingly, under these conditions the reaction presents a



Scheme 9.2 1,3-Dipolar cycloaddition reaction of phenyl azide **22** and phenylacetylene **23** in the presence of capsule $\mathbf{21}_2$. Partially reproduced with permission from Reference [25]. Copyright 2002 (Wiley-VCH).



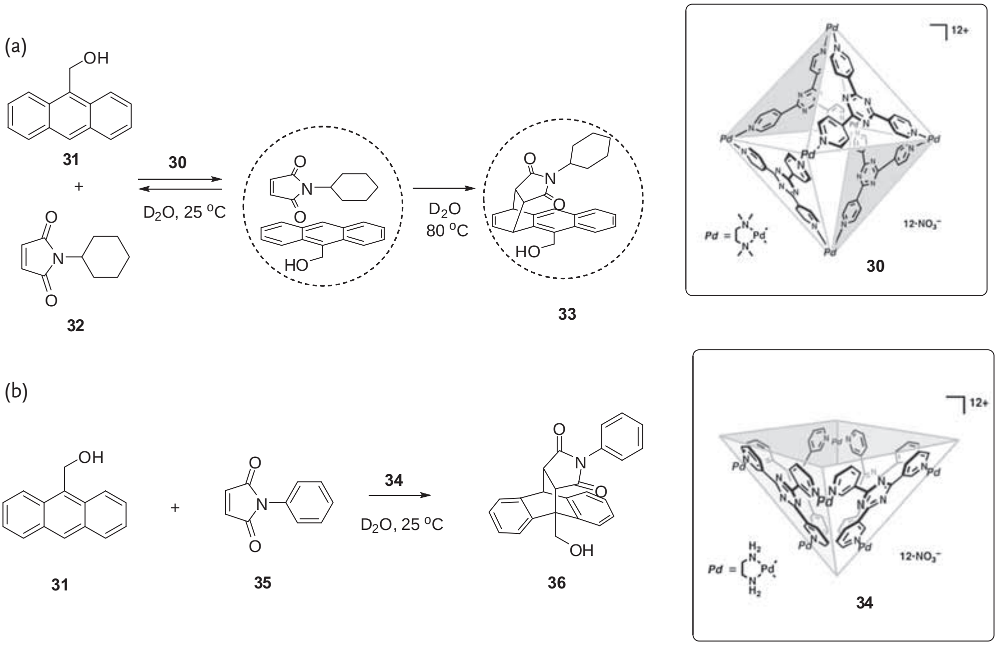
Scheme 9.3 Diels–Alder reaction between **25** and **26** (a) or **28** (b) in the presence of capsule $\mathbf{24}_2$. Partially reproduced with permission from Reference [25]. Copyright 2002 (Wiley-VCH).

complete regioselectivity, with exclusive formation of the 1,4-isomer, which is simply released from the "nanoreactor" after denaturation with DMF. The presence of a confined space for the reaction participants induces a specific orientation of the substrates, which is responsible for the high regioselectivity. In the absence of the capsule, the 1,5- and 1,4-regioisomeric triazoles are formed in a 1 : 1 ratio. In addition, these capsules are highly size-selective and different aromatic substrates with incompatible sizes gave no reaction. The main limit of this system, which is more frequently observed for encapsulation catalysts, lies in the inability of the system to display turnover.

The same problem was encountered during the study of a Diels–Alder reaction between *p*-benzoquinone (**25**) and cyclohexadiene (**26**) in the presence of capsule $\mathbf{24}_2$ (Scheme 9.3) [27, 28]. This system is a closed-shell capsule of approximately spherical shape, composed of two concave building blocks. When a mixture of the reactants was added to the capsule, only encapsulation of the quinone was observed. Cyclohexadiene was apparently encapsulated only in very small – yet sufficient – amounts, because the encapsulated product **27** of the Diels–Alder reaction was formed slowly over time. A 200-fold rate acceleration was observed in the presence of the capsule over the control reaction. Product inhibition prevented real turnover and therefore this capsule did not truly act as a catalyst. True catalysis was subsequently observed when cyclohexadiene **26** was replaced by the sterically more-demanding thiophene dioxide derivative **28.** In this case the product **29** of the Diels–Alder reaction with benzoquinone is expelled from the cavity as a result of its lowered affinity for the capsule [29].

Fujita and coworkers reported recently on a positively charged cage (**30**) as an efficient catalyst for a Diels–Alder reaction in water [30]. The structure presents an octahedral $[M_6L_4]^{12+}$ coordination cage composed of six *cis*-protected square-planar Pd^{2+} complexes and four triangular tridentate triazine-based ligands, providing a well-structured hydrophobic pocket for the encapsulation of two different substrates (Scheme 9.4a). The investigated reaction between 9-hydroxymethylanthracene (**31**) and *N*-cyclohexylmaleimide (**32**) provides an unexpected regio- and stereoselectivity leading to the exclusive formation of the *syn*-isomer of 1,4-adduct **33**. However, also in this case the high affinity of the product for the cavity prevents a catalytic turnover. This issue was overcome by using a square-pyramidal bowl (**34**) that allows a facile substrate release thanks to its open structure (Scheme 9.4b). In addition, the affinity of the cavity for the substrates, based on aromatic interactions, is lower for product **36** compared to the reagents, permitting an efficient turnover and the use of catalytic amount of bowl **34**. Interestingly, the different orientation of substrates in the cage leads to a complete reversal of regioselectivity in favor of 9,10-adduct **36**.

A final, beautiful example of a catalytically active capsule has been reported by Raymond and coworkers, based on the supramolecular tetrahedral cage **37** (Figure 9.6a) [31]. The catalytic system is based on a highly charged, water-soluble structure with a hydrophobic cavity able to thermodynamically stabilize protonated substrates. This permits the usually acidic hydrolysis of orthoformates under basic



Scheme 9.4 (a) Encapsulation of 9-hydroxymethylanthrancene **31** and *N*-cyclohexylmaleimide **32**, within cage **30** and the subsequent Diels–Alder reaction leading to the *syn* isomer of 1,4-adduct **33** within the cavity of **30**; (b) catalytic Diels–Alder reaction of 9-hydroxymethylanthracene **31** and *N*-phenylmaleimide **35** in an aqueous solution of **34**, leading to 9,10-adduct **36**. Partially reproduced with permission from Reference [30]. Copyright 2006 (AAAS).

“bulk” conditions, mimicking the ability of enzymes to create local environments with a different pH. The proposed mechanism involves an initial pre-equilibrium of the neutral substrate with the cavity, followed by its protonation inside the capsule, presumably picking up a proton from water (Figure 9.6b). Subsequent hydrolysis within the cavity liberates two equivalents of the corresponding alcohol and the protonated formate ester. This ester dissociates from the capsule and undergoes further basic hydrolysis in solution. The system showed a high efficiency and size selectivity, catalyzing the quantitative hydrolysis of various orthoformates in the presence of only 1 mol% catalyst at pH 11.

The examples provided here certainly show how the field of self-assembled nanocapsules is becoming a promising tool for the development of efficient and highly selective catalysts, thanks to the high versatility in terms of size, shape, and interactions of the cavities. In particular, the confinement imposed by the encapsulating structure provides an attractive tool for inducing the formation of less-favored regioisomers or alteration of the bulk physicochemical properties.

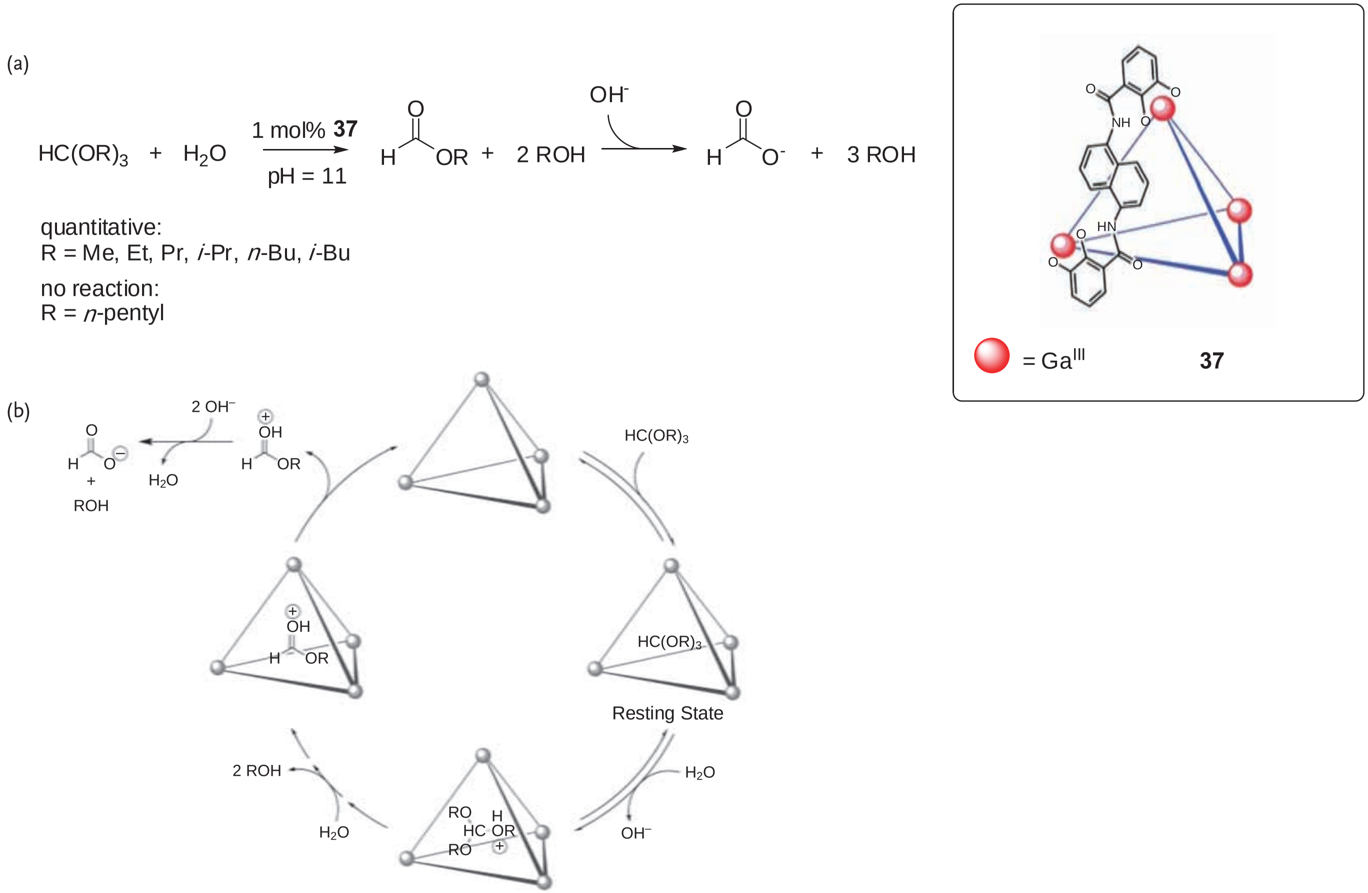


Figure 9.6 (a) Reaction and substrate scope for orthoformate hydrolysis in the presence of catalytic **37**; (b) proposed reaction mechanism. Partially reproduced with permission from Reference [31]. Copyright 2007 (AAAS).

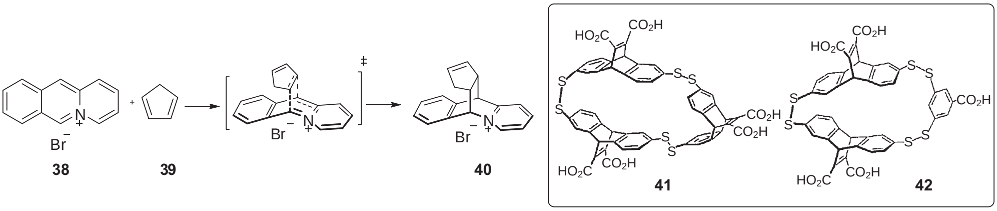
9.3
Self-Selected Catalysts

The successful development of the self-assembled catalysts discussed in Section 9.2.1 has been strongly aided by the presence of highly functional covalent analogs, which could serve as design models. From this perspective, the development of catalysts without a priori knowledge of their structural requisites is highly challenging. In such a case, three issues are of crucial importance for catalyst discovery. Firstly, a combinatorial library of potential organocatalysts has to cover a large part of chemical space. In other words, the members should have a large structural and functional variety. Secondly, ideally the chemical reaction of interest itself should identify the best-suited catalyst. Alternatively, in cases were screening of the reaction is not feasible, the transition state of the reaction needs to be used as the target. Similar to the strategy used for the development of catalytic antibodies, catalysts can be identified based on their ability to stabilize the transition state of a reaction [32]. Thirdly, given the fact that subtle changes in a catalyst can dramatically affect its efficiency or selectivity [33], the screening methodology should be highly sensitive to small changes in energy. In this section we illustrate the potential of dynamic chemistry in such a project.

9.3.1
Dynamic Combinatorial Chemistry

Dynamic combinatorial chemistry (DCC) has emerged as an attractive approach for the rapid formation of combinatorial libraries of potential receptors, materials, and also catalysts [34, 35]. In a dynamic combinatorial library (DCL) the members are formed through reversible bond formation between the constituent molecules. Potentially, libraries of this type cover a large chemical space, determined by the structural information embedded in the constituent molecules in terms of chemical function and ability to form reversible bonds. The reversibility of the connecting bonds, which can be either covalent or non-covalent, implies that exchange between the library members is possible. Consequently, the composition of the DCL is determined by the overall thermodynamic energetic minimum of the library. The attractive feature lies in the fact that this minimum changes upon exposure of the DCL to an external stimulus, for example, the addition of a target. The target interacts with the library members and changes the thermodynamic landscape of the library. Being dynamic, the DCL will adapt and alter its composition, ideally increasing the concentration of the library member that interacts most strongly with the target. Numerous examples have now illustrated that dynamic combinatorial screening can yield highly effective receptors, enzyme inhibitors, adaptive materials, and sensors [36]. The application of DCC for catalyst development has so far been rather limited.

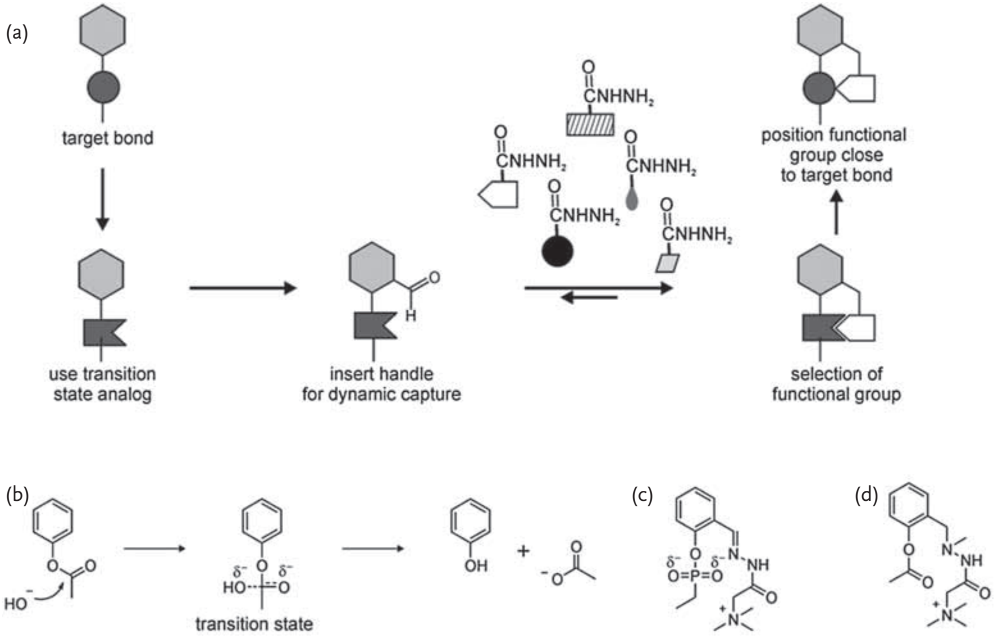
As a first example, Sanders, Otto, and coworkers described the isolation of a catalyst for the Diels–Alder reaction between acridizinium bromide (**38**) and cyclopentadiene (**39**) (Scheme 9.5) [37]. A DCL composed of a series of macrocycles was obtained by mixing three dithiol building blocks. Considering that the transition state of a Diels–Alder reaction is very similar to the product, the product **40** itself was used as a transition state analog (TSA) and added as a template to the DCL. A significant shift in library composition was observed in favor of two macrocycles, **41** and **42** (Scheme 9.5). After isolation, it was indeed found that both macrocycles had a high affinity for the product (and thus, supposedly, the transition state). However, a comparison with the binding affinities for the substrate showed that only macrocycle **41** bound the product more strongly than the starting material, indicating that only **41** would exhibit catalytic activity. Measurements of the rates of the Diels–Alder reaction in the presence and absence of **41** and **42** indeed revealed an accelerating effect (~10×) for macrocycle **41** and no effect for **42.** Although rather modest in terms of efficiency, this study is of importance as it showed for the first time the self-selection of a catalyst from a DCL. In a follow-up study the same group applied the same principle to select a catalyst for an acetal hydrolysis reaction [38].



Scheme 9.5 Diels–Alder reaction between acridizinium bromide **38** and cyclopentadiene **39**, and macrocycles **41** and **42** self-selected by the product **40**.

Prins, Scrimin, *et al.* have illustrated the potential of dynamic covalent capture for catalyst development (Figure 9.7a) [10]. Inspired by enzymes that operate according to a covalent catalysis mechanism, they focused on the self-selection of functional groups that can assist intramolecularly in the cleavage of a flanking ester bond [39].

2-Ethylphosphonoxybenzaldehyde was chosen as the target molecule, containing the phosphonate group as transition state analog for the basic cleavage of an ester moiety and an aldehyde for reversible hydrazone formation (Figure 9.7b). Exposure of this target to a library of functional hydrazides yielded a mixture of the corresponding hydrazones, some of which were stabilized through intramolecular interactions between the phosphonate and the functional group of the hydrazide unit. The occurrence of intramolecular interactions emerges immediately from a comparison of the library distribution with the distribution of a reference library in which the target is absent (using 2-methoxybenzaldehyde).


(a)
target bond
use transition state analog
insert handle for dynamic capture
CNHNH₂
position functional group close to target bond
selection of functional group
(b)
HO
transition state
OH
(c)
(d)

43

44

Figure 9.7 (a) Schematic illustration of the application of dynamic covalent capture for catalyst discovery; (b) target reaction; (c) selected functional group by the phosphonate transition state analog; and (d) positioning of the selected group near the target bond.

Analytical protocols based on ^1H–^{13}C HSQC NMR spectroscopy [40] and UV-Vis-spectroscopy [41] were developed to rapidly determine the mixture composition. Comparison of the relative hydrazone concentrations in both libraries revealed the strongest amplification for hydrazone **43** equipped with an ammonium group. Positioning of that ammonium close to the ester moiety in functionalized phenyl acetate **44** indeed resulted in an enhanced cleavage rate. A series of control experiments supported the hypothesis that this was indeed due to transition state stabilization.

These two examples illustrate the potential of informative chemical systems: the desired information (transition state stabilization) is obtained by analyzing the response of such a system to the addition of a target (transition state analog). The potential of systems chemistry emerges even more strongly from the following example that was reported by the group of Philp [42]. The novelty of their approach was the coupling of Darwinian evolution in a dynamic library with self-replication processes. They took a small four-component dynamic library of two imines and two nitrones able to interconvert (Figure 9.8a). At thermodynamic equilibrium, a 1.0 : 1.4 : 1.7 : 1.0 composition was observed for compounds **45–48**, respectively. These components were chosen because of two characteristics. Two

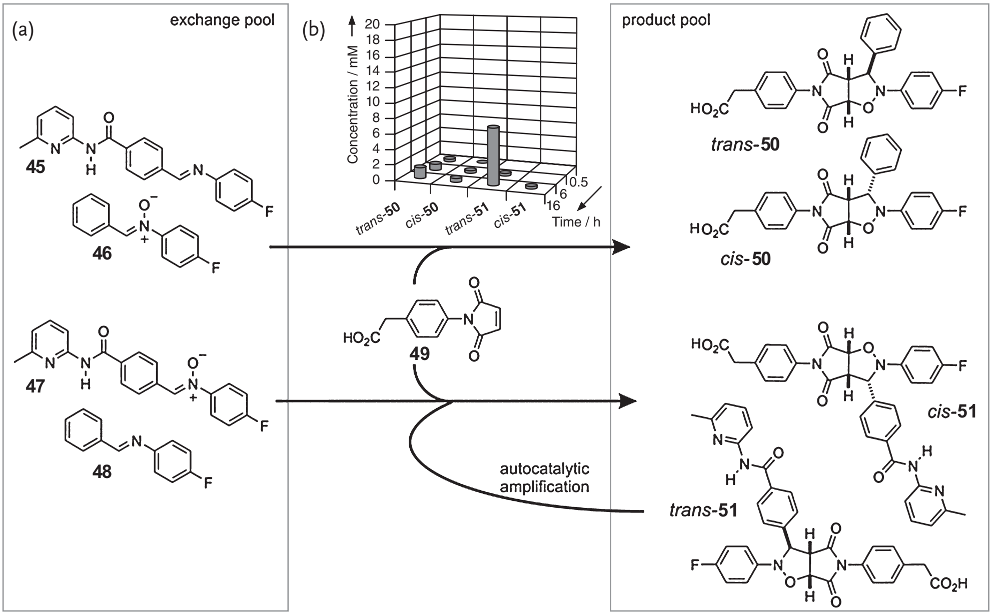


Figure 9.8 (a) Self-amplification of a replicator from a dynamic imine/nitrone library; (b) distribution in the product pool after reaction with maleimide **49**. Partially reproduced with permission from Reference [42]. Copyright 2008 (Wiley-VCH).

components of the library (**45** and **47**) contain an amido pyridine unit that can complex a carboxylic acid through the formation of two hydrogen bonds. Two components (**46** and, importantly, again **47**) are nitrones able to undergo a 1,3-dipolar cycloaddition with maleimides. The addition of maleimide **49**, containing a carboxylic acid, to this dynamic mixture gives a spectacular result. The maleimide reacts with both nitrones **46** and **47** and causes an irreversible transfer of material to a product pool forming two pairs of diastereomeric cycloadducts: *cis*- and *trans*-**50** and *cis*- and *trans*-**51**, respectively. The special effect is caused by *trans*-**51**, which is able to catalyze its own formation through the ternary complex [**47**•**49**•*trans*-**51**]. So, whereas *trans*-**51** is initially formed through the bimolecular reaction between **47** and **49**, the autocatalytic pathway takes over progressively. As a consequence, nitrone **47** is depleted from the library at a much higher rate compared to **46**. Being dynamic, the library responds by shifting its composition towards the formation of more nitrone **47**. Both the process of self-replication and evolution work in the same direction and highly efficiently drive the system towards the formation of *trans*-**51**. After 16 h and an overall conversion of 48%, *trans*-**51** constitutes almost 80% of the product pool (Figure 9.8b). In contrast, for a reference maleimide lacking the carboxylic acid recognition module a conversion of only 21% was obtained in the same time interval, with a rather uniform distribution of the four diastereomeric products.

9.4
Conclusions

Non-covalent interactions are intrinsic to catalysis. Catalytic efficiencies and selectivities are determined by subtle energy differences occurring between catalyst and substrate(s) along the reaction coordinate. However, the examples discussed in this chapter illustrate that non-covalent interactions can also play an important role in catalysis when they are remote from the active site. Self-assembly of catalytic subunits may result in the formation of catalytic complexes with an activity or selectivity that is superior to that of the sum of the single components. In addition, large varieties of such complexes are spontaneously formed upon mixing the appropriate subunits. Since the covalent synthesis is restricted to the subunits, this is an attractive way to prepare combinatorial libraries with a structural complexity that would be difficult to achieve using other methods. Alternatively, self-assembly may be used to construct cage-like catalytic structures. Such structures are able to mimic some essential features displayed by enzymes, such as substrate binding and effective concentration enhancement, together with the creation of local chemical environments that differ from the bulk. Frequently, these systems suffer from product inhibition, but recent progress in this exciting area has shown that this hurdle can be overcome by the use of cages that represent an “open” face or that are kinetically labile.

Finally, the emergence of dynamic combinatorial chemistry and systems chemistry has conceptually changed the way in which catalyst discovery can be approached. Dynamic combinatorial chemistry allows virtual libraries to be generated that can cover a large amount of chemical space. The ability of these libraries to spontaneously adapt to a stimulus allows for self-selection that partly relieves the burden of rational catalyst design. An integrated approach including evolving dynamic combinatorial libraries and an extensive use of recognition motifs for self-assembly of the catalyst, the substrate, *and* the transition state may lead to unprecedented catalytic systems.

Acknowledgments

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Part I
Asymmetric Catalysis with Non-Covalent Interactions

10

Brønsted Acids

Yunus E. Türkmen, Ye Zhu, and Viresh H. Rawal

10.1

Introduction

Much of this introductory section is taken from our review on the same subject that appeared in the earlier edition of this volume [1]. Chiral phosphoric acids and chiral thioureas, each representing a major subdivision of hydrogen bonding catalysis, are discussed in separate chapters, the former by Professor Akiyama (Chapter 11) and the latter by Professor Schreiner (Chapter 12).

The importance of hydrogen bonding in chemical and biological systems has been recognized in the scientific community for many years, as this ubiquitous interaction is one of the central forces in nature. Whereas individual hydrogen bonds are relatively weak compared to covalent bonds, collectively they can be of enormous importance. Apart from the crucial role that hydrogen bonds play in mediating the life-sustaining properties of water, they are found to be essential for maintaining the form and function of most biological systems [2]. Hydrogen bonds are important for the organization and base pairing of DNA and RNA, the secondary and tertiary structure of proteins [3], small molecule recognition [4], and the catalytic cycles of various enzymes [5, 6]. Despite the many vital functions fulfilled by hydrogen bonds in biological systems, until recently they had been little utilized for the promotion of chemical reactions. This omission may have been due, in part, to the limited understanding of the reactivity-enhancing properties associated with hydrogen bonding and the hesitation to use what is recognizably a weak bonding interaction when other more established methods for catalysis were already available. Over the past dozen years, this situation has changed dramatically, and many enantioselective reactions have been developed in which chiral hydrogen-bond donors serve as catalysts. This chapter provides a summary of the progress in this rapidly expanding field.

The historical recognition of hydrogen bonding is as nebulous as the phenomenon itself. Records dating back to the early 1900s allude to the observation of hydrogen bonding in various chemical systems. These interactions were referred to using non-specific terms such as “inner complex building,” “weak union,” and “chelation” [7]. It was not until 1931, in Pauling’s seminal paper on the nature of

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the chemical bond, that the term “hydrogen bond” was coined [8]. Even in 1936, research pioneers such as Huggins used the term “hydrogen bridge” [9] to describe the phenomenon of water’s affinity to itself [10] and to carbohydrates, proteins, and other biological molecules [11, 12]. In *Nature of the Chemical Bond*, Pauling defined the hydrogen bond as the favorable interaction that develops between a donor (A-H) and an acceptor (B) as a result of the relative electronegativities of “A” and “B” [13]. The shared electrons in the covalently bonded “A-H” are drawn to the more electronegative “A,” leaving the hydrogen atom partially deshielded of electrons. The hydrogen bond acceptor “B” typically possesses a lone pair of electrons or polarizable π electrons to interact with the deshielded hydrogen. Since only one covalent bond to the 1s orbital of hydrogen is optimal, the additional bonding interaction between “H” and “B” is considered to be ionic in character.

Unlike covalent bonds, which have a relatively narrow distribution of energies, lengths, and geometries within particular groupings of bonding partners, the analogous properties can vary dramatically in hydrogen bonds. One finds countless variations in bond strengths and geometric orientations with hydrogen bonds, even within the same bonding partners. To simplify the matter, hydrogen bonds have been grouped into three different categories: strong, moderate, and weak (Table 10.1) [7]. “Strong” hydrogen bonds are nearly covalent in nature, having linear bond angles and bond distances that are shorter than the sum of the van der Waals radii of “A” and “B.” More common are hydrogen bonds that fall under the “medium” category, and include interactions such as that between two water molecules. Further down the spectrum, “weak” hydrogen bonds can be as weak as van der Waals forces and can have nearly perpendicular directionality with respect to the acceptor, with bonding distances far in excess of the van der Waals radii of the two atoms involved. The different forms of hydrogen bond interactions can be classified under the Lewis definition of acids and bases, where the hydrogen-bond donor (A–H) is defined to be a Lewis acid, and the hydrogen bond acceptor (B), a Lewis base. As such, hydrogen bond catalyzed reactions represent a subset of Lewis acid catalyzed reactions. The strength of a hydrogen-bond donor is well correlated to its pK_a, although environmental factors, such as solvation, temperature, and dielectric constants, can also affect the nature of a hydrogen bond.

Table 10.1 Jeffrey’s classification of strong, moderate, and weak hydrogen bonds [7].

	Bonding strength		
	Strong	**Moderate**	**Weak**
A—H•••B interaction	Mostly covalent	Mostly electrostatic	Electrostatic
H↔B bond length (Å)	~1.2–1.5	~1.5–2.2	~2.2–3.2
A↔B bond length (Å)	~2.2–2.5	~2.5–3.2	~3.2–4.0
Bond angle AHB (°)	175–180	130–180	90–150
Bond energy (kcal mol^{-1})	14–40	4–15	<4

Figure 10.1 Hydrogen bonding continuum.

Given the infinite variations in bonding patterns, hydrogen bonding is best considered as a continuum of bonding interactions, from weak to strong. Moving further along this spectrum, past even strong hydrogen bonds, there is the further possibility of full proton transfer between the hydrogen-bond donor and acceptor, with the donor now being considered a Brønsted–Lowry acid (Figure 10.1). Viewed in this capacity, the proton is unquestionably the most widely used catalyst for chemical reactions, utilized for the promotion of whole families of organic reactions. With catalyzed enantioselective reactions, however, the traditional Brønsted acid description may not be appropriate, particularly given the non-polar solvents used for such reactions. To transfer chirality from the catalyst to the substrate, the chiral anion must be well ordered and, very likely, be tightly coordinated to the conjugate acid through one or more strong hydrogen bonds, supplemented by other interactions. As such, even strong hydrogen-bond donors, conventionally referred to as Brønsted acids, may be better thought of in the Lewis acid sense, capable of forming “very strong” hydrogen bonds, rather than as traditional Brønsted acids. Concepts of proton affinities and acidity/basicity associated with Brønsted acids may also be applied to systems that form hydrogen bonds [14]. The hydrogen bond itself can be considered a “frozen” stage of a proton transfer reaction, in which each of the three bonding categories in Table 10.1 describes a different stage along the proton transfer spectrum.

Despite its prevalence in biological and chemical systems, hydrogen bonding had been little used before the turn of the century as a design principle for asymmetric catalysts. These interactions can be weak and variable, such that catalyst–substrate interactions based on hydrogen bonding are expected to be disrupted easily at ambient temperatures. The electrostatic nature of these interactions also makes them responsive to changes in solvent polarity. Unlike traditional metal-based Lewis acid catalysts, which have well-defined metal–ligand coordination geometries, hydrogen bonds exhibit a much broader distribution of donor–acceptor geometric orientations. Moreover, the distance between a hydrogen-bond donor and acceptor is typically longer than that observed in many metal-based Lewis acid–Lewis base complexes, and this is expected to result in less effective chirality transfer. Similar issues of asymmetric induction arise in conceptualizing the design of a strongly acidic chiral catalyst, as the design must account for enantiofacial discrimination using what is essentially an achiral H^+ in the presence of a chiral anion. Solvent effects are particularly important for such “chiral proton” catalysts, since effective chirality transfer requires that the chiral counter-ion be held in close proximity, as a well-organized tight-ion pair. The wide variability observed in the strength and bonding geometries of hydrogen bonds provides not only unique challenges for catalyst design but also offers opportunities for the discovery and development of new concepts in catalysis.

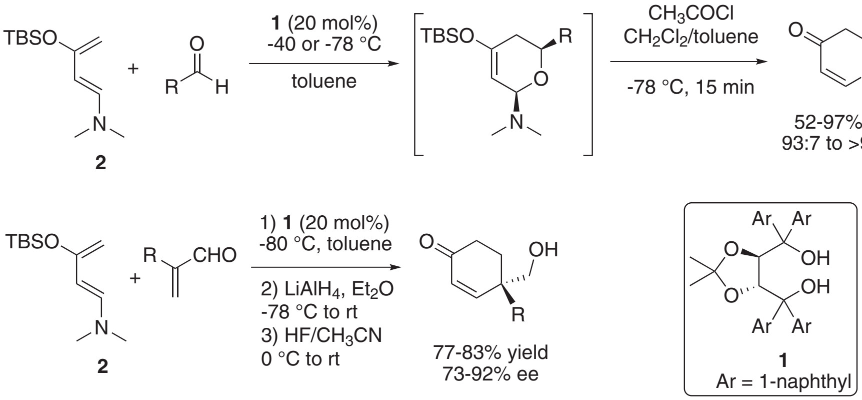
The systematic use of hydrogen bonding for the promotion of racemic organic reactions began most noticeably in the 1980s, as summarized below. More recent developments on asymmetric catalysis of organic reactions using hydrogen bonds, the focus of this chapter, are presented in the next section [15–27]. In a seminal contribution, Hine and coworkers showed that hydrogen bonding with 1,8-biphenylene diols could effectively activate epoxides to nucleophilic attack [28, 29]. Kinetic experiments showed that both hydroxyl groups, in their respective locations on the catalyst scaffold, were important for achieving maximum rates of epoxide opening. Kelly and coworkers found that achiral biphenylene-diols, at 40–50 mol% catalyst loading, significantly accelerated the Diels–Alder reaction of cyclopentadiene with various acroleins [30]. The rate increase is ascribed to activation of the carbonyl group by the diol, via two hydrogen bonds. Through a series of elegant co-crystallization studies, the Etter group showed that achiral diaryl ureas form well-defined crystalline complexes with a number of carbonyl-containing compounds. The stability of the complex derives from a two-point hydrogen bond between the urea N–H bonds and the carbonyl oxygen [31–33]. The first report on the application of Etter's concept of using ureas as Lewis acids was by Curran and coworkers, who showed that the outcome of radical allylation reactions and Claisen rearrangements can be altered by the presence of ureas and thioureas [34–36]. Contemporaneously, Rawal and Eschbach examined the use of electron-deficient diaryl ureas for the promotion of a Diels–Alder reaction between cyclopentadiene and methyl vinyl ketone. Although the ureas clearly accelerated the cycloaddition reaction, the rate increase was only modest (~twofold with 10% catalyst) [A. Eschbach and V.H. Rawal (1994), The Ohio State University, unpublished results]. In a key publication, Schreiner and Wittkopp reported in 2002 a study on the use of Etter-type ureas for promotion of Diels–Alder reactions [37, 38]. Etter ureas have also been used by Takemoto and coworkers for the activation of nitrones towards the addition of TMSCN and ketene silyl acetals [39]. A full discussion of the developments in the use of such ureas as catalysts, particularly for enantioselective synthesis, is presented in Chapter 12 by Schreiner.

Several other classes of hydrogen-bond donors have also been used as catalysts to promote organic reactions. The early reports provide a clear demonstration of the ability of hydrogen-bond donors to function as Lewis acids and thereby promote organic reactions. Formation of a hydrogen bond to the electrophile (such as a carbonyl or an imine), through either a one-point or two-point interaction, enhances the reactivity of the electrophile. In this regard, hydrogen bond formation functions in the same way as traditional metal-based Lewis acids, effectively lowering of the LUMO energy level of the electrophile, thereby making it more reactive to the second reactant, whether a nucleophile or a diene.

The development of chiral hydrogen-bond donors that function as catalysts for enantioselective organic reactions has been the focus of innumerable studies over the past dozen years, detailed in hundreds of publications. One of the earliest successes in this area was from the Jacobsen laboratory, realized in the course of screening a library of metal complexes of salicylaldehyde imines as catalysts for the Strecker reaction. These workers observed that the free ligands themselves, rather than their complexes with Lewis acidic metals, catalyzed the cyanide addition to aldimines and keto-imines with high enantioselectivities [40, 41]. An optimized, peptide-like thiourea catalyst afforded α-aminonitrile products in 65–92% yield and up to 91% enantiomeric excess. Modification of the initial catalyst resulted in the development of an effective asymmetric hydrocyanation reaction of keto-imines. In a separate development, while investigating the accelerating effect of hydrogen bonding to a carbonyl group [42], Rawal and coworkers showed that the simple chiral diol taddol catalyzed highly enantioselective cycloaddition reactions between amino dienes and carbon- and hetero-dienophiles [43, 44]. Also critical to the rapid development of hydrogen-bonding catalysis is a report by Takemoto and coworkers [45], whose elegantly simple, easily prepared, and remarkably effective chiral thioureas served to open the floodgates to a sea of asymmetric reactions. Finally, the near simultaneous development of chiral phosphoric acids by Akiyama's group [46] and Terada's group [47] laid the foundation for the development of chiral Brønsted acid catalysis. The above set of reports sparked the imagination of synthetic chemists around the world, and within a short time the field of hydrogen-bonding/Brønsted acid catalysis mushroomed. Leading laboratories from around the globe have entered this field and have reported numerous highly enantioselective transformations catalyzed by chiral hydrogen-bond donors. The sections that follow provide a summary of the many developments in hydrogen bond catalyzed enantioselective reactions, along with a discussion of their mechanisms and selectivity models. As noted above, phosphoric acids, each representing substantial subsets of hydrogen bonding, are discussed in separate chapters later in this volume.

10.2
Chiral Alcohol Catalysts

A clear demonstration that simple, chiral hydrogen bond donors can induce high enantioselectivity in reactions was reported in 2002 by Rawal and coworkers [48, 49]. In connection with their studies on the Diels–Alder reactivity of amino-siloxy dienes, these authors observed that the hetero-Diels–Alder reactions of such dienes proceeded more rapidly in chloroform (~10–30×) than in other common aprotic organic solvents, even polar solvents [42]. The rate difference was greater still in alcohols. The authors attributed the higher rates in chloroform and alcohols to hydrogen-bond activation of carbonyl oxygen by either the polar C–H bond of chloroform or the O–H bond of alcohols. The hydrogen-bond catalysis was rendered enantioselective by using a chiral alcohol as a hydrogen bond donor catalyst. Thus in early 2003, Rawal and coworkers reported that the tartrate-derived chiral diol, taddol (α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol), catalyzed the hetero-Diels–Alder reaction of aldehydes with excellent enantioselectivities [43, 48, 49]. The commercially-available diol 1-naphthyl-taddol (**1**) catalyzed the hetero-Diels–Alder reactions of amino-siloxy diene **2** with aromatic and aliphatic aldehydes to afford, after acetyl chloride treatment, dihydropyrone derivatives in good to high yields and excellent enantiomeric ratios (Scheme 10.1). This work represented one of the first highly enantioselective reactions (>90% ee) and the first highly enantioselective cycloaddition reaction catalyzed by a chiral hydrogen-bond donor. The method was later extended to the enantioselective Diels–Alder reaction of diene **2** with α,β-unsaturated aldehydes, enabling the efficient formation of cyclohexenone derivatives containing a quaternary chiral center [44].



Scheme 10.1 Enantioselective Diels–Alder and hetero-Diels–Alder reactions catalyzed by taddol **1**.

A model based on crystal structures of taddols as a starting point was put forth to rationalize the high enantioselectivities obtained through taddol catalysis (Figure 10.2) [44, 50, 51]. In the solid state, taddols exist in well-defined seven-membered ring conformations, with one of the hydroxyls internally-hydrogen bonded to the other and opposing pairs of aryl groups in pseudo-axial and pseudo-equatorial orientations. Assuming the same arrangement in solution, then the free hydroxyl, which is expected to be more acidic, can form a strong, one-point hydrogen bond to the dienophile carbonyl. The resulting activated carbonyl is expected to be further stabilized by donor–acceptor (π*–π) interactions with the electron-rich distal ring of the naphthalene unit. This electrostatic interaction serves not only to increase the population of the activated aldehyde, but also to block one face of the aldehyde. A crystal structure of a taddol–aldehyde complex lent support to parts of the proposed model (Figure 10.3). The taddol-catalyzed hetero-Diels–Alder reaction has also been the focus of computational studies by the groups of Deslongschamps, Houk, and Ding and closely related models have been proposed to explain the observed enantioselection [52–56].

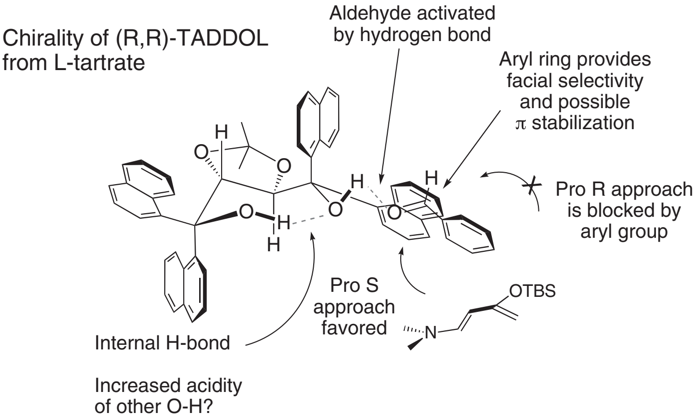


Figure 10.2 Proposed model for the taddol-catalyzed hetero-Diels–Alder reaction.

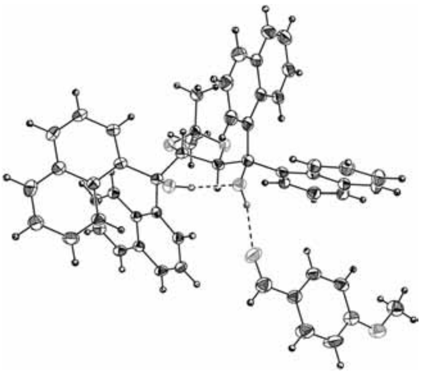
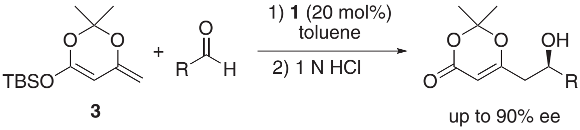
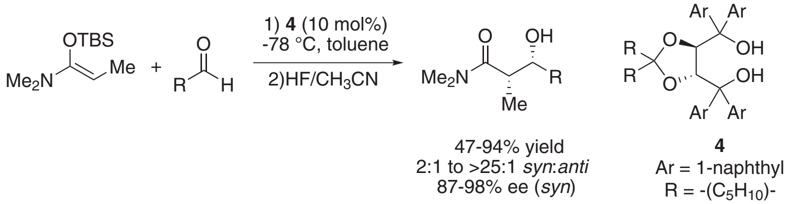


Figure 10.3 X-Ray crystal structure of the H-bonded complex of *rac*-**1** and *p*-anisaldehyde.

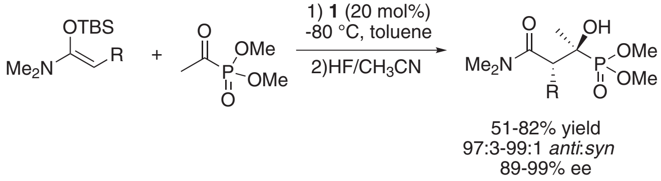
Taddol was also found to be a highly effective H-bonding catalyst for the Mukaiyama and related reactions. The vinylogous Mukaiyama aldol reaction of diene **3** with various aldehydes catalyzed by taddol **1** afforded the aldol products in up to 90% ee (Scheme 10.2) [57]. It was subsequently reported that the Mukaiyama aldol reaction of *O*-silyl-*N,O*-ketene acetals with aldehydes exhibited high levels of diastereo- and enantioselectivity when taddol **4** was used as the H-bonding catalyst in 10 mol% loading (Scheme 10.3) [58]. β-Hydroxy amide products were obtained in high yields and *syn*/anti selectivity as well as excellent enantiomeric excesses (87–98% ee). Slightly lower enantioselectivities were obtained when using the commercially available naphthyl-taddol **1**. It was also shown that Schwartz's reagent reduced the amide products directly to the corresponding aldehydes, with little epimerization of the α-stereocenter. The taddol catalysis methodology was further extended to the Mukaiyama aldol reactions of *O*-silyl-*N*,*O*-ketene acetals with acylphosphonates (Scheme 10.4) [59]. With the use of the commercially available taddol **1** as the H-bonding catalyst, α-hydroxy-phosphonate products were obtained in excellent diastereo- (*anti*/*syn*) and enantioselectivities (89–99% ee). Acetyl cyanide was found to be compatible with the above method, affording quaternary silylated cyanohydrin products in high ee's. Finally, the enantioselective Mukaiyama aldol reaction of α-ketoesters with *O*-silyl-*N*,*O*-ketene acetals was achieved recently via H-bonding catalysis [60].



Scheme 10.2 Enantioselective vinylogous Mukaiyama aldol reaction catalyzed by taddol **1**.

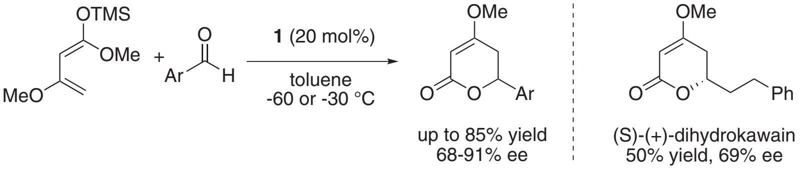


Scheme 10.3 Enantioselective Mukaiyama aldol reaction of *O*-silyl-*N*,*O*-ketene acetals.



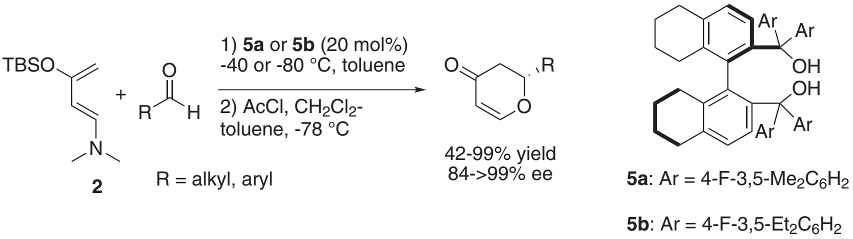
Scheme 10.4 Enantioselective Mukaiyama aldol reactions of acyl phosphonates.

Taddol catalysis of cycloadditions can be extended to other reactive dienes. Ding and coworkers showed in 2004 that taddol **1** was capable of catalyzing the cycloaddition of Brassard's diene with various aromatic aldehydes to give δ-lactone products directly on reaction workup (Scheme 10.5) [61]. The products were obtained in good yields (up to 85%) and good to high enantioselectivities (68–91% ee). The methodology was applied to the synthesis of the natural product (S)-(+)-dihydrokawain, which was obtained in 50% yield and 69% ee. The same researchers also investigated the catalysis of the hetero-Diels–Alder reaction between Danishefsky's diene and benzaldehyde with taddol derivatives; the dihydropyrone product was obtained in moderate yields and up to 77% ee [56].



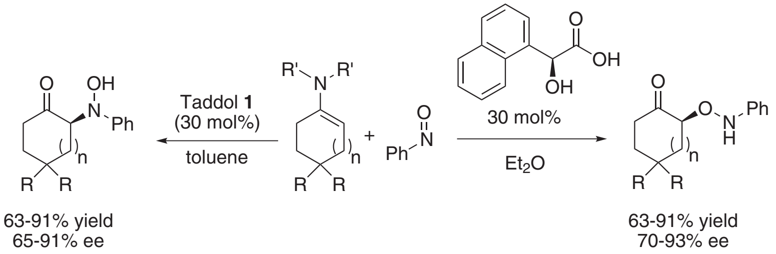
Scheme 10.5 Enantioselective hetero-Diels–Alder reaction of Brassard's diene catalyzed by taddol **1**.

Not surprisingly, alcohols other than taddols are capable of catalyzing enantioselective reactions, although this area remains relatively unexplored. A collaborative effort between the Rawal and Yamamoto groups led to the development of axially chiral 1,1′-biaryl-2,2′-dimethanols (e.g., **5**, BAMOLs) as hydrogen-bond donor catalysts (Scheme 10.6) [62]. Several variations of these novel diols were prepared and examined as catalysts for the hetero-Diels–Alder reactions between amino siloxy diene **2** and various aldehydes. Of the BAMOLs examined, compounds **5a** and **5b** were shown to be the most effective catalysts, affording cycloadducts in moderate to high yields (42–99%) and generally excellent enantioselectivities (84–>99% ee). Significantly, high enantioselectivity was observed even when the carbonyl component was acetaldehyde (97% ee) or 2-butynal (98% ee). In both of these examples, the catalyst enables remarkable discrimination between the prochiral faces of an aldehyde carbonyl, given that the α-carbons in both have small steric demands.



Scheme 10.6 Enantioselective hetero-Diels–Alder reaction catalyzed by BAMOL **5**.

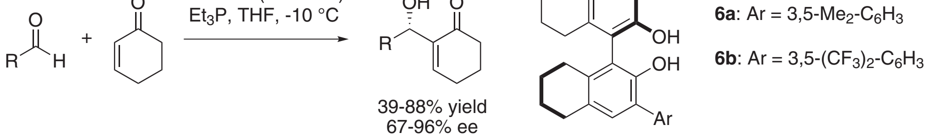
A crystal structure of 1,1′-biphenyl-BAMOL and benzaldehyde revealed the presence of an intramolecular hydrogen bond between the two hydroxyl groups of the catalyst and an intermolecular hydrogen bond to the carbonyl of benzaldehyde, similar to what was observed in the crystal structure of a taddol–aldehyde complex (Figure 10.3). Yamamoto and coworkers reported in 2005 an elegant application of catalyst and substrate-controlled reversal of regioselectivity in the enantioselective nitroso aldol reaction of enamines (Scheme 10.7) [63]. The use of (*S*)-1-naphthyl glycolic acid as the H-bonding catalyst afforded the *O*-nitroso aldol products whereas the use of taddol **1** was exclusively *N*-selective. Notably, in addition to the catalyst used, the structures of the enamines have a large effect on the regiochemical outcome of the reaction. Computational studies were carried out to rationalize the observed regio- and enantioselectivity of this reaction [64].



Scheme 10.7 Regio- and enantioselective nitroso aldol reaction of enamines.

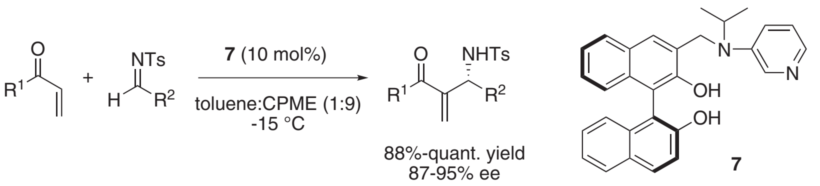
An early example of chiral alcohol-based hydrogen bonding catalysts is the work by Braddock and coworkers in which they used paracyclophanediols (PHANOLs) as dual H-bond donors [65, 66]. Significant rate enhancements were obtained in the Diels–Alder reactions of dienes with α,β-unsaturated aldehydes and ketones and in the epoxide-opening reactions with amines. However, little or no asymmetric induction was obtained when a chiral PHANOL catalyst was used.

In 2003, Schaus and coworkers utilized Binol-derived hydrogen-bond donors **6a** and **6b** along with triethylphosphine in the enantioselective Morita–Baylis–Hillman reaction of cyclohexenone with various aldehydes (Scheme 10.8) [67]. Control experiments showed that the use of mono-methylated diols resulted in significant decreases in both the yields and enantioselectivities.



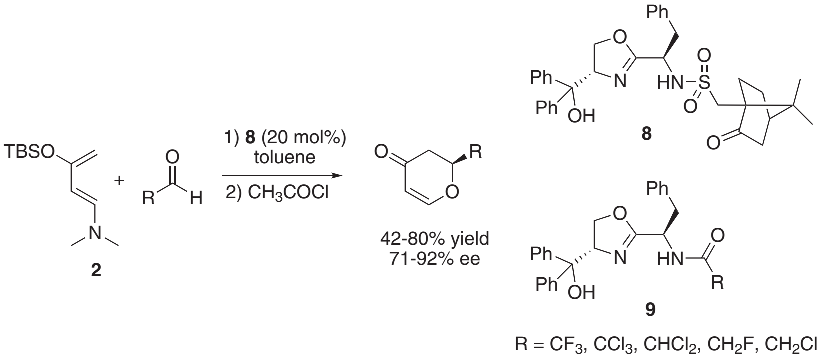
Scheme 10.8 Enantioselective Morita–Baylis–Hillman reaction.

The Binol-based bifunctional catalyst **7** was used by Sasai and coworkers in 2005 in the enantioselective aza-Morita–Baylis–Hillman reaction of α,β-unsaturated aldehydes and ketones with *N*-sulfonyl imines (Scheme 10.9) [68]. The spacer between the Binol and the pyridine moieties as well as the position of the amino group were varied systematically and catalyst **7** was found to be the most effective, affording the Morita–Baylis–Hillman products in high yields and enantioselectivities.



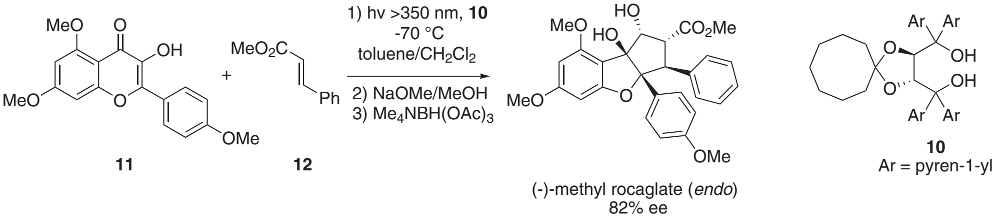
Scheme 10.9 Enantioselective aza-Morita–Baylis–Hillman reaction catalyzed by **7**.

In 2005, Sigman and coworkers introduced catalyst **8** as a new H-bonding catalyst based on an oxazoline template (Scheme 10.10) [69]. The sulfonamide moiety was designed as the modular site, and an examination of different sulfonyl groups revealed catalyst **8** with a camphor-sulfonamide group as the most effective catalyst, in terms of both yield and enantioselectivity, for the hetero-Diels–Alder reaction of diene **2** with aldehydes. In their continuing studies, the same research group investigated the effect of the acidity of the amide group in catalyst **9** and the effect of the electronic nature of the aldehyde substrates on the rate and enantioselectivity of the reaction through detailed kinetic studies [70, 71].



Scheme 10.10 Enantioselective hetero-Diels–Alder reaction.

Porco and coworkers used taddol **10** as a chiral H-bond donor in the asymmetric photochemical [3+2] cycloaddition between oxidopyrylium betaine generated from **11** and methyl cinnamate **12** (Scheme 10.11) [72]. (–)-Methyl rocaglate was obtained



11

12

(-)-methyl rocaglate (*endo*)
82% ee

10
Ar = pyren-1-yl

Scheme 10.11 Asymmetric photochemical [3+2] cycloaddition.

in 82% ee after the photochemical [3+2] cycloaddition followed by a base-mediated α-ketol rearrangement and reduction. The product could be obtained in 94% ee with 86% recovery from the mother liquor after recrystallization.

In addition to the studies mentioned above, chiral alcohols have been used as H-bonding catalysts in a vinylogous aldol reaction of Chan's diene with aldehydes [73], in an enantioselective Strecker reaction [74], and in the enantioselective addition of aza-enamines to imines [75]. Taddol has also found use as a "memory of chirality" enhancer in the stereoselective synthesis of β-lactams from amino acid derivatives [76, 77].

10.3
Chiral Squaramides as Hydrogen-Bond Donor Catalysts

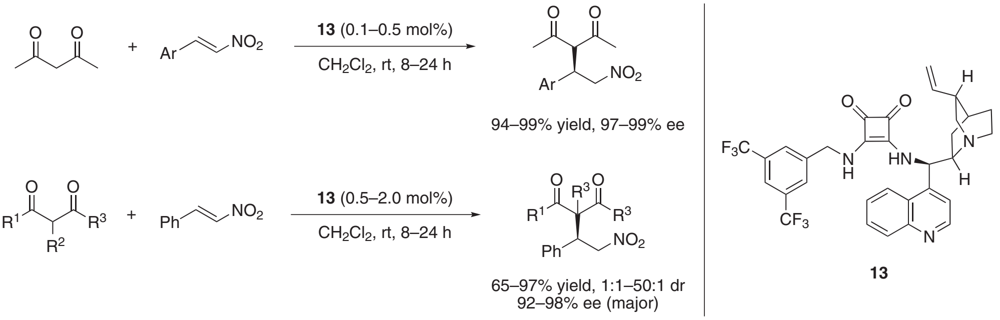
10.3.1
Introduction

In the field of catalysis by hydrogen bond donors, catalysts that operate by a single H-bond interaction with the electrophile, such as taddols, are unique. Typically, multiple H-bonding contacts are necessary to activate, organize, and differentiate the prochiral faces of a reactant. Among catalysts capable of multiple hydrogen bonds, those based on the thiourea motif have dominated the field. Scores of thiourea catalysts have been developed and these have proven successful in various enantioselective transformations (Chapter 12). Despite the many structural variations that have been examined with chiral thiourea catalysts, and likewise with the related guanidinium catalysts, what has remained constant is the activating unit, which consists of two N–H groups connected by one carbon. The distance between the two donor hydrogens in all these catalysts is fixed at ca. 2.1 Å.

With a desire towards exploring scaffolds with larger distances between the two donor hydrogens, Rawal and coworkers reported in late 2008 the development of bis-amides of squaric acid as potential hydrogen bonding catalysts [78, 79]. Squaramides are prepared from simple precursors through a modular assembly, involving two sequential addition–elimination reactions between dialkoxysquarate and two amines/anilines. This simple synthesis allows the preparation of numerous chiral catalysts, with varying steric and electronic properties. An important difference between squaramides and thioureas (and likewise, with guanidines, amidines, aminopyridines, etc.) is that the two hydrogen atoms are approximately one-third further apart in squaramides. Given their ease of preparation, unique structural features, and the initial successes in enantioselective reactions, chiral squaramides have generated much interest. Since the first report of chiral squaramide catalysts less than four years ago, there are already dozens of reports on the use of squaramide catalysts for enantioselective reactions. Squaramide-based catalysts have proven to be remarkably effective in promoting a wide range of synthetically useful enantioselective transformations, rivaling those obtained by other catalysts [80]. A summary of the many chiral squaramide catalyzed enantioselective reactions is provided below.

10.3.1.1 **Michael Addition Reaction Involving Nitroalkenes**

The first report on the development and use of chiral squaramide derivatives as hydrogen-bond donor catalysts appeared in 2008 by Rawal and coworkers [78]. The authors showcased the usefulness of this new scaffold by evaluating the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes, the same reaction that was used to illustrate the capability of a thiourea catalyst by Takemoto [45]. Of the catalysts examined, the cinchonine-derived squaramide **13** functioned well as a bifunctional catalyst and provided the conjugate addition product in high yield and excellent enantioselectivity (Scheme 10.12). Less reactive substrates such as α-substituted 1,3-dicarbonyl compounds also participate in the desired reaction. The low catalyst loading (as low as 0.1 mol%) demonstrated the remarkably high catalytic activity of squaramide catalyst **13**. This work established the squaramide unit as an effective scaffold on which to build chiral H-bond donor catalysts.



Scheme 10.12 Michael addition of 1,3-dicarbonyl compounds to nitroalkenes.

Subsequently, several groups have studied related squaramide-catalyzed enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkenes. High enantioselectivities have been achieved using pyrrolidine-cinchonine-squaramide catalyst **14** [81], quinine-squaramide catalyst **15** [82, 83], and C_3-symmetrical cinchonine-squaramide catalyst **16** (Figure 10.4) [84]. Notably, the reaction time

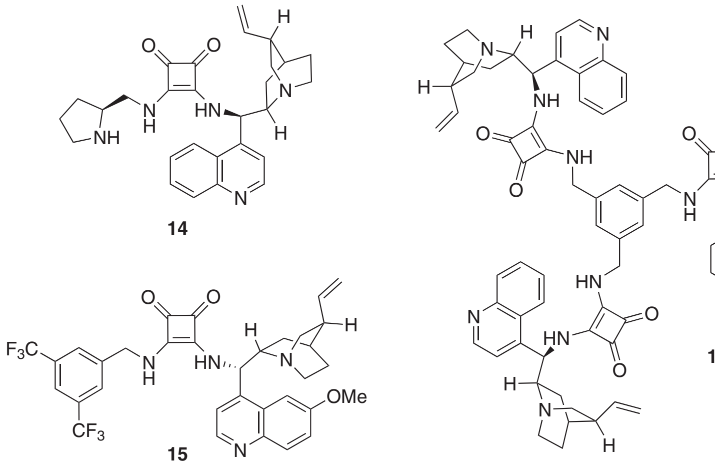
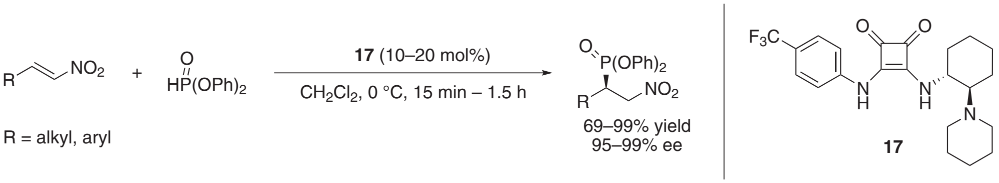


Figure 10.4 Squaramide catalysts used for Michael additions to nitroalkenes.

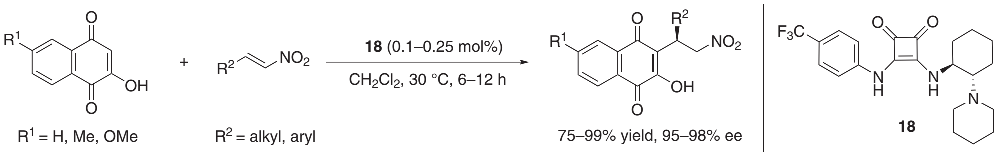
can be reduced to few minutes without loss of enantioselectivity by running the reaction in brine or a ball-mill using quinine-squaramide catalyst **15**. Additionally, C_3-symmetrical cinchonine-squaramide catalyst **16** can be recovered by simple precipitation and used for six cycles without loss of selectivity and activity. Given the expected mode of activation, the function of the two additional squaramide units remains unclear.

To further demonstrate the utility of chiral squaramides, Rawal and coworkers reported Michael addition reaction of diphenyl phosphite to nitroalkenes [85]. A series of 1,2-diaminocyclohexane-derived squaramides were developed and examined as catalysts. Among these, the piperidine-derived catalyst **17** proved remarkably effective and afforded the phospha-Michael addition product in good to high yield and uniformly excellent enantioselectivity (Scheme 10.13). Both aliphatic- and aromatic-substituted nitroalkenes, including those bearing acidic protons or sterically-demanding substituents, were found to be suitable substrates. The resulting chiral β-nitrophosphonates are precursors to biologically active β-aminophosphonic acids. The excellent results obtained for the different Michael reactions point to the unique capability of the squaramide scaffold as compared to other types of catalysts and many more enantioselective Michael reactions have been developed using squaramides.



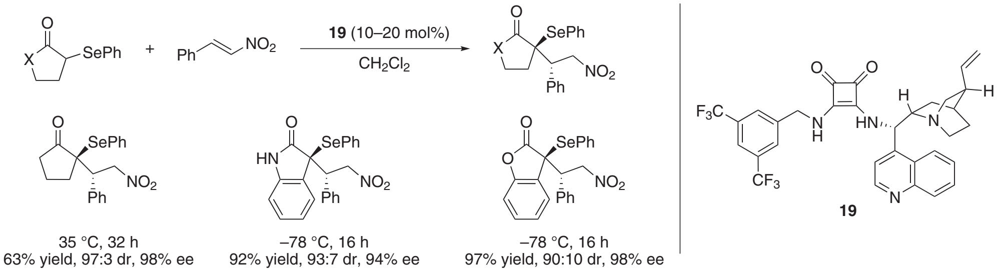
Scheme 10.13 Michael addition of diphenyl phosphite to nitroalkenes catalyzed by **17**.

Quinones and naphthoquinones are important structural units in many natural products and drugs. The redox properties of the quinone pharmacophore influence various regulatory cellular processes, and for this reason quinones have been the subjects of intense studies. Du and coworkers have developed a highly enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes catalyzed by squaramide **18** (Scheme 10.14) [86]. Starting with both aliphatic- and aromatic-substituted nitroalkenes, this transformation afforded a range of chiral functionalized-naphthoquinones in high yields and high enantioselectivities under mild reaction conditions and using low catalyst loading. The same group had earlier reported the corresponding thiourea-catalyzed reaction, with many examples giving 99% ee [87].



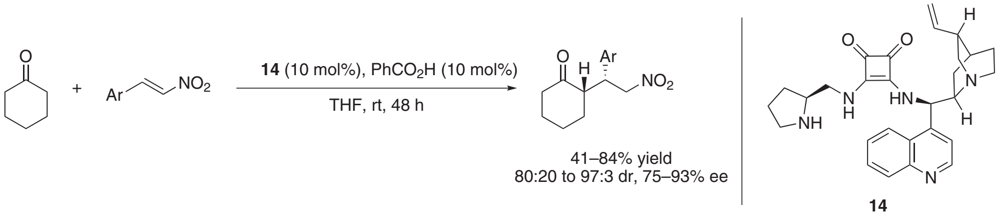
Scheme 10.14 Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes.

Alemán and Marini *et al.* have discovered that thiourea-catalyzed addition reactions of α-selenoindanones to nitroalkenes proceed with high enantioselectivity; however, thiourea catalysts showed poorer activity and selectivity when applied to other α-selenocarbonyl substrates, such as α-selenocyclopentanone [88]. On the other hand, squaramide-based catalysts proved highly effective in catalyzing these reactions, yielding the corresponding Michael adducts in very good diastereo- and enantioselectivities (Scheme 10.15). Additionally, by using a cinchonidine-derived squaramide and a cinchonine-derived squaramide, they were able to access both enantiomers of the products. This squaramide-catalyzed transformation provided a new approach for the synthesis of various enantiomerically enriched α-alkyl-α-phenylselenylcarbonyl compounds, and illustrated the differences between the catalytic capacities of thiourea and squaramide catalysts.



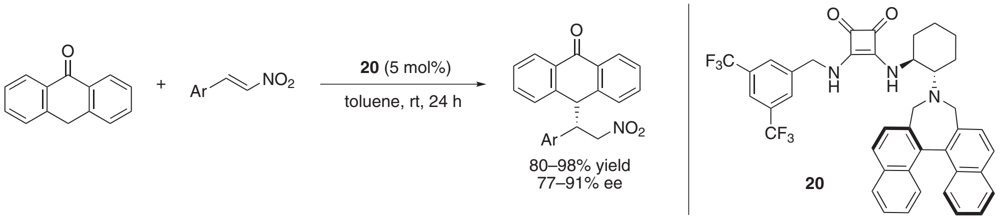
Scheme 10.15 Michael addition of α-selenocarbonyl compounds to nitroalkenes.

Dong and coworkers have developed a pyrrolidine-cinchonine-squaramide catalyst for enantioselective Michael addition of ketones to nitroalkenes (Scheme 10.16) [81]. The assembly of two privileged chiral motifs, pyrrolidine and cinchonine, with a squaramide core enabled the catalyst in promoting the addition of both cyclohexanone and 1,3-diketones to aryl-substituted nitroalkenes, providing the corresponding products in modest to high diastereo- and enantioselectivities. The authors pointed out that the match between the chiralities of pyrrolidine and cinchonine is important for the high enantioselectivity.


O
Ar
NO2
14 (10 mol%), PhCO2H (10 mol%)
THF, rt, 48 h
O H Ar
NO2
41–84% yield
80:20 to 97:3 dr, 75–93% ee
O O
NH
N H
HN
H
N
H
N
14

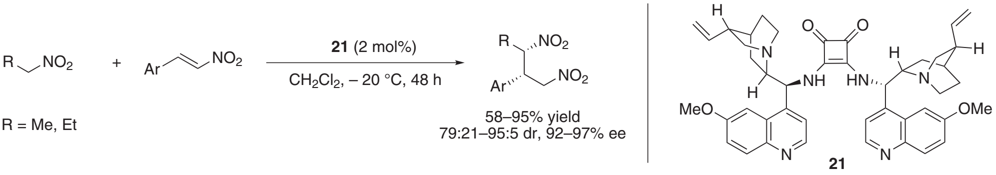
Scheme 10.16 Enantioselective Michael addition of cyclohexanone to nitroalkenes.

Kim and coworkers have developed a binaphthyl-modified chiral squaramide (**20**) bearing both central and axial chiralities [89]. The Michael addition of anthrone to nitroalkenes catalyzed by squaramide **20** afforded the products in high yield and good enantioselectivity (Scheme 10.17). Notably, the reaction at lower temperature (0 °C) resulted in a reduced enantioselectivity. This transformation has also been shown to be catalyzed by cinchona alkaloid and thiourea derivatives [90–92].



Scheme 10.17 Enantioselective Michael addition of anthrone to nitroalkenes.

Du and coworkers have developed a stereoselective direct Michael addition of nitroalkanes to nitroalkenes catalyzed by quinine-derived dimeric squaramide **21** [93]. This transformation provided facile access to 1,3-dinitro compounds in high diastereo- and enantioselectivities starting from aryl-substituted nitroalkenes (Scheme 10.18). However, the use of an aliphatic nitroalkene as Michael acceptor resulted in a low yield and diminished enantioselectivity. While nitroethane and 1-nitropropane are excellent substrates, branched 2-nitropropane did not undergo the Michael addition reaction. The authors also noted that slightly reduced dias-

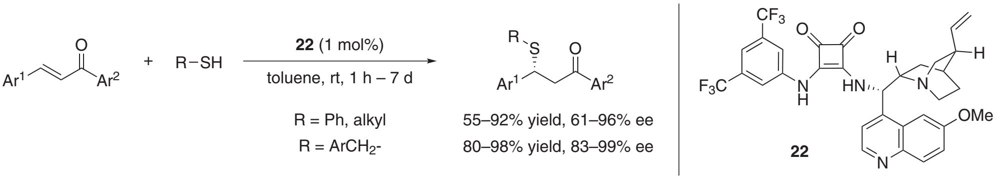


Scheme 10.18 Enantioselective Michael addition of nitroalkanes to nitroalkenes.

tereo- and enantioselectivities were obtained with a high (10 mol%) catalyst loading, which was ascribed to the self-association of the catalyst under concentrated conditions. The Michael adduct can be reduced to a synthetically useful chiral 1,3-diamine and further transformed into a chiral cyclic thiourea. Other catalysts such as cinchona alkaloids and chiral thioureas are also known to catalyze this reaction [94–96].

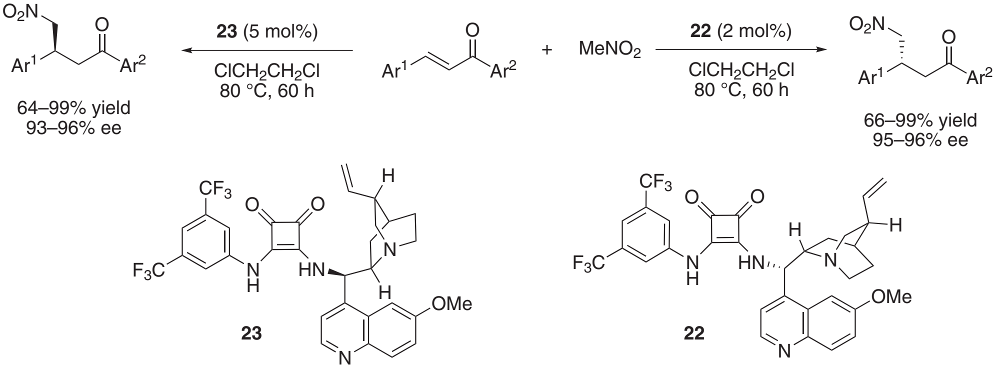
10.3.1.2 Michael Addition Reaction Involving *trans*-Chalcones

Enantioselective Michael reactions of thiols provide a convenient route to diverse chiral sulfides. Chen and coworkers have demonstrated that a chiral squaramide catalyst was effective in promoting a sulfa-Michael conjugated addition of various aromatic and aliphatic thiols to a wide range of *trans*-chalcones (Scheme 10.19) [97]. Moderate to excellent yields and enantioselectivities were achieved. Notably, the reactions between various benzylthiol and *trans*-chalcones bearing electron-donating or electron-withdrawing substituents proceeded with high enantioselectivities.



Scheme 10.19 Enantioselective Michael addition of thiols to chalcones.

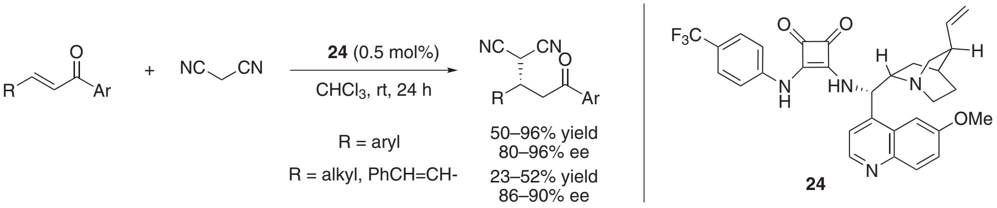
The enantioselective Michael addition of nitroalkanes to enones provides an attractive synthetic route towards chiral pyrrolidines, γ-lactams, and γ-amino acids. Du and coworkers have developed a squaramide-catalyzed Michael addition reaction of nitroalkanes to chalcones (Scheme 10.20) [98]. The authors noted that electron-withdrawing substituents on the aryl portion of squaramide enhanced the activity of the catalyst owing to the increased acidity of the squaramide N–H. Interestingly, the yield and enantioselectivity both increased when the reaction was performed at an elevated temperature. The reactions between nitromethane and various chalcones afforded the Michael adducts in high yields and high enantioselectivities at 80 °C. Varying the substituents on chalcones showed some effect on



Scheme 10.20 Enantioselective Michael addition of nitroalkanes to chalcones.

yield but had little influence on the enantioselectivity. Importantly, both enantiomers of the products can be obtained using either a quinidine-derived or a quinine-derived squaramide catalyst. While no reaction occurred for 1-phenyl-2-buten-1-one, 2-cyclohexen-1-one furnished the product with modest enantioselectivity. The reaction between chalcone and nitroethane afforded the product in high enantioselectivity, albeit with modest yield and low diastereoselectivity.

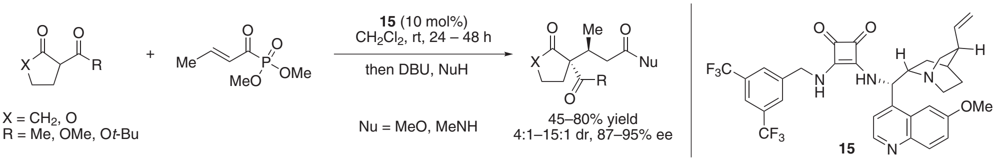
Du and coworkers recently reported the enantioselective Michael addition of malononitrile to *trans*-chalcones using a quinine-derived squaramide-catalyst (Scheme 10.21) [99]. Interestingly, slightly improved yield and enantioselectivity were obtained when the catalyst loading was lowered from 10 to 0.5 mol%. The authors attributed the lower enantioselectivity at high catalyst concentration to self-association of the catalyst. Starting from chalcones bearing electron-withdrawing or electron-donating substituents, or heterocycles as aryl groups, a wide array of γ-cyano carbonyl compounds were obtained in good to high enantioselectivities with low catalyst loading under mild reaction conditions. Moreover, aliphatic enones afforded the Michael adducts in good enantioselectivity, albeit in lower yields.



Scheme 10.21 Enantioselective Michael addition of malononitrile to chalcones.

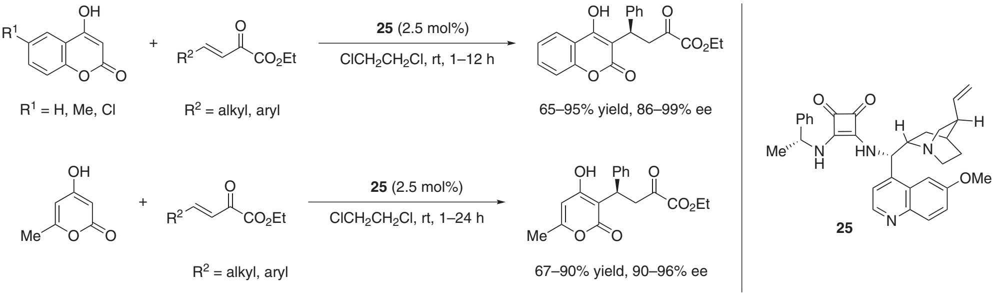
10.3.1.3 Michael Addition Reaction Involving Other C=C Michael Acceptors

α,β-Unsaturated acylphosphonates are attractive Michael acceptors because the acylphosphonates are readily converted into a corresponding amide or ester upon treatment with an alcohol or amine in the presence of a base. Jørgensen and coworkers have studied Michael addition of different nucleophiles to α,β-unsaturated acylphosphonates [100]. Initial screening indicated that thiourea catalysts were ineffective in inducing the reaction when cyclic 1,3-dicarbonyl compounds were employed as nucleophiles. In contrast, squaramide catalyst **15** was found to be quite effective in promoting the reactions between α,β-unsaturated acylphosphonates and cyclic 1,3-diketones, 1,3-ketoesters, and lactones, affording the Michael adducts in high diastereo- and enantioselectivities (Scheme 10.22).

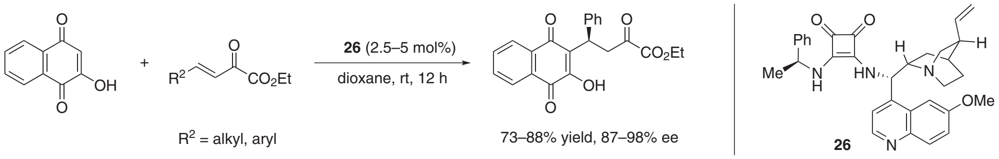


Scheme 10.22 Enantioselective Michael addition to α,β-unsaturated acylphosphonates.

Xu and coworkers have explored squaramide-catalyzed conjugate addition reactions using β,γ-unsaturated α-ketoesters as Michael acceptors [101, 102]. The authors discovered that chiral squaramide catalysts **25** and **26** consisting of two chiral subunits are effective in promoting reactions between β,γ-unsaturated α-ketoesters and various nucleophiles, including 4-hydroxycoumarins, 4-hydroxypyrone, and naphthoquinones (Schemes 10.23 and 10.24). Both γ-(hetero)aryl- and γ-alkyl-α-ketoesters are suitable substrates, and afforded a series of Michael adducts in modest to high yields and high enantioselectivities. The authors noted that in contrast to squaramide catalysts, the equivalent thiourea catalysts performed poorly, affording the products in low yield and



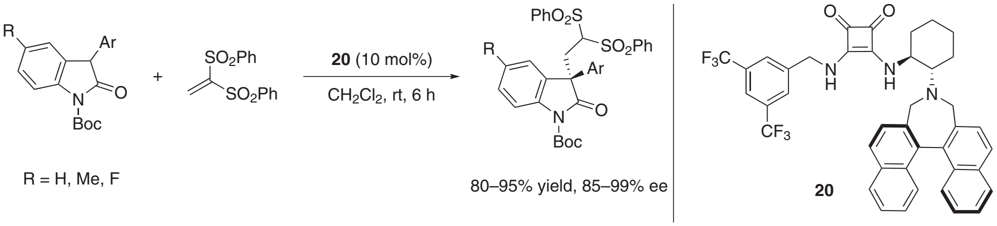
Scheme 10.23 Enantioselective Michael reactions catalyzed by squaramide **25**.



Scheme 10.24 Enantioselective Michael reactions catalyzed by squaramide **26**.

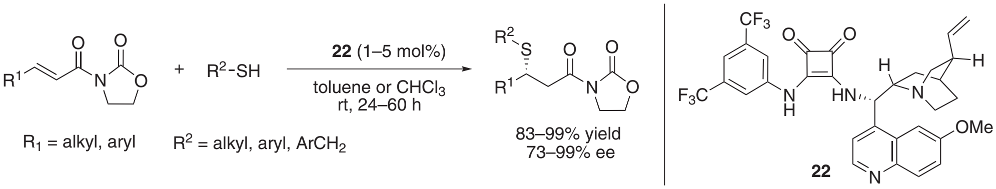
enantioselectivity. Based on calculated results of the interactions between α-ketoester and squaramide or thiourea, the authors found that the γ-position of β,γ-unsaturated α-ketoester is more electrophilic when hydrogen-bonded with squaramide than with thiourea, which is consistent with the experimental results [101].

Indoles and oxindoles represent core structures of many natural products and bioactive molecules. Construction of oxindoles bearing a C3 quaternary stereocenter is of great interest owing to their existence in various biologically and pharmaceutically active chemicals. Kim and coworkers have developed an organocatalytic enantioselective conjugate addition of 3-substituted oxindoles to vinyl sulfones [103]. While a thiourea catalyst was effective in promoting the reactions of 3-alkyl-substituted oxindoles, a binaphthyl-modified chiral squaramide (**20**) was found to be superior in catalyzing the reactions between 3-aryl-substituted oxindoles and vinyl sulfones (Scheme 10.25). Various synthetically useful 3,3-disubstituted oxindoles were obtained in high yield and enantioselectivity under mild reaction conditions.



Scheme 10.25 Enantioselective conjugate addition of oxindoles to vinyl sulfones.

Following their report on squaramide-catalyzed enantioselective conjugate addition of thiols to chalcones, Chen and coworkers explored the sulfa-Michael addition to α,β-unsaturated *N*-acylated oxazolidinones [104]. The same quinine-derived squaramide **22** catalyzed the reactions between a broad range of thiols to various α,β-unsaturated *N*-acylated oxazolidinones, giving addition products in good yields and high enantioselectivities (Scheme 10.26). The X-ray crystal structure of catalyst **22** revealed that the intermolecular hydrogen bonds between the catalyst molecules are mediated by water. Considering the possible effect of water, the authors found that addition of 4 Å molecular sieves improved the reproducibility of the

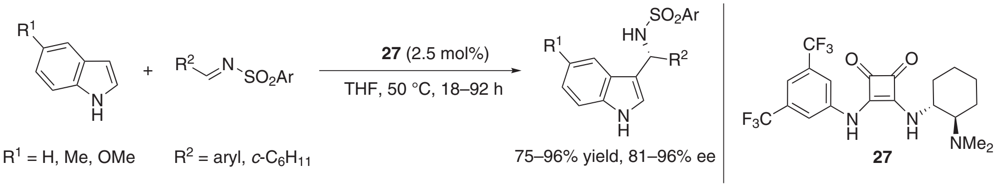


Scheme 10.26 Enantioselective conjugate addition reactions of thiols catalyzed by **22**.

reactions involving thiophenols. Treatment of the Michael adduct with MeMgBr–MeOH afforded corresponding enantio-enriched β-sulfurated ester without diminution of enantiopurity.

10.3.1.4 Reactions Involving a C=N Bond

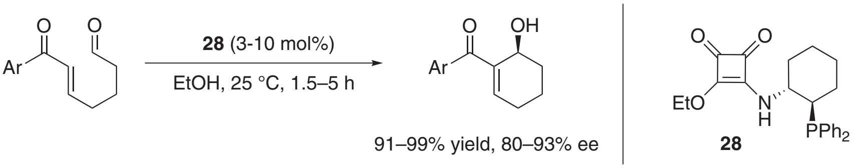
In an effort to demonstrate a different facet of squaramide's capability, Zhao and Rawal *et al.* have successfully developed a squaramide-catalyzed enantioselective Friedel–Crafts reaction of indoles with imines (Scheme 10.27) [105]. To overcome the slow reaction rate at room temperature, the authors performed the reactions at an elevated temperature. Notably, the reaction at 50 °C afforded the desired product in much improved yield with only a slight decrease in enantioselectivity. Using 2.5 mol% cyclohexanediamine-derived squaramide catalyst **27**, the reactions between various indoles and a diverse range of *N*-arylsulfonyl imines of both electron-rich and electron-deficient aromatic as well as aliphatic aldehydes proceeded with high yield and high enantioselectivity. This transformation represents an efficient synthesis of enantioenriched indolyl-sulfonamides.



Scheme 10.27 Enantioselective Friedel–Crafts reaction of indoles with sulfonyl imines.

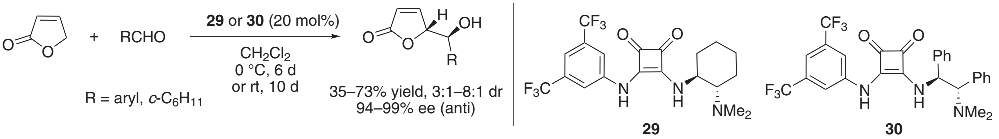
10.3.1.5 Reactions Involving a C=O Bond

Wu and coworkers have developed phosphine-squaramate-catalyzed enantioselective intramolecular Morita–Baylis–Hillman reactions [106]. Utilizing a chiral squaramate containing tertiary phosphine as catalyst (**28**), a wide range of ω-formylenones was converted into the cyclic hydroxyl enones in high yield and high enantioselectivity (Scheme 10.28). The reaction afforded low yield and selectivity when the corresponding phosphine-squaramide or phosphine-amide was used as a catalyst. The authors noted that the phosphine-squaramate catalyst provided a better enantioselectivity than the phosphine-thiourea analog [107].



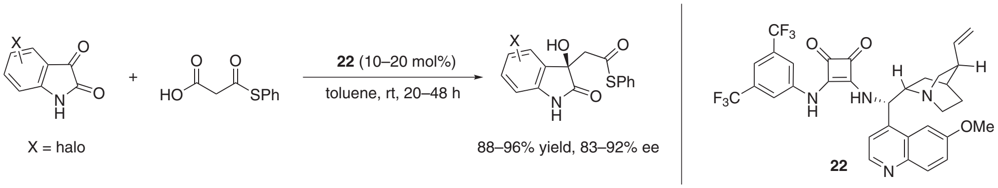
Scheme 10.28 Enantioselective intramolecular Morita–Baylis–Hillman reaction.

The direct vinylogous aldol reactions of γ-crotonolactone provided efficient access to chiral 5-substituted-2(5*H*) furanones (γ-butenolides), as opposed to the less direct route involving the vinylogous Mukaiyama aldol reactions of siloxyfurans. Pansare and coworkers have developed a squaramide-catalyzed asymmetric direct vinylogous aldol reaction of γ-crotonolactone with aldehydes [108]. The authors examined a range of thiourea and squaramide catalysts for this reaction and found the cyclohexanediamine- and stilbene-diamine-derived squaramides **29** and **30** to be optimal in achieving high enantioselectivity (Scheme 10.29). Under mild reaction conditions, various aldehydes, including aromatic aldehydes bearing electron-donating and -withdrawing groups, as well as cyclohexanecarboxaldehyde, underwent the desired reaction in modest diastereoselectivity and high enantioselectivity.

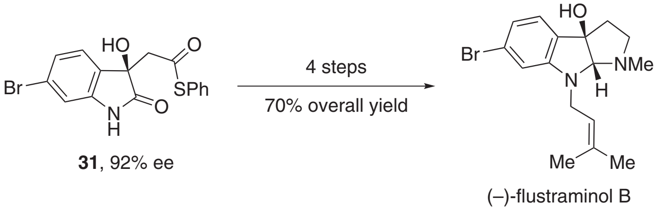


Scheme 10.29 Direct vinylogous aldol reaction of γ-crotonolactone with aldehydes.

Shibata and coworkers have developed the first enantioselective decarboxylative addition to isatins by malonic acid half-thioesters as enolate equivalents [109]. Having screened various types of organocatalysts for enantioselective addition of malonic acid half-(phenyl)thioester to 4,6-dibromoisatin, the authors found that while proline derivative, quinine, and quinine-derived thiourea provided low enantioselectivity (<40% ee) both the cyclohexanediamine- and quinine-derived squaramides yielded the product in good enantioselectivity (>80% ee). A range of halo-substituted isatins participated in the squaramide-catalyzed reaction, affording the decarboxylative adducts in high yield and enantioselectivity (Scheme 10.30). Although the reactions of isatin and 6-bromoisatin proceeded with modest enantioselectivity, the enantiopurity of these products can be improved by recrystallization. The authors demonstrated the first enantioselective synthesis of (−)-flustraminol B, proceeding through four steps starting from the decarboxylative addition product **31** (Scheme 10.31).



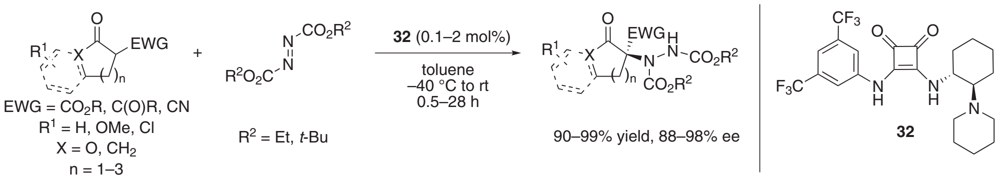
Scheme 10.30 Decarboxylative addition of malonic acid half-thioesters to isatins.



Scheme 10.31 Enantioselective synthesis of (−)-flustraminol B.

10.3.1.6 **Reactions Involving a N=N Bond**

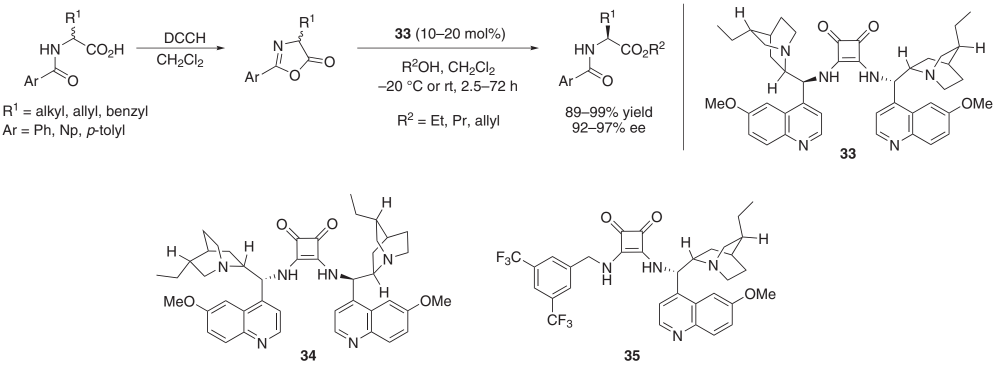
Rawal and coworkers have developed an enantioselective α-amination reaction of 1,3-dicarbonyl compounds [110]. In the presence of squaramide catalyst **32**, the reactions using azodicarboxylates as the electrophilic aminating reagent proceeded smoothly, affording the corresponding α-hydrazinated 1,3-dicarbonyl compounds (Scheme 10.32). An extensive range of substrates, including cyclic β-ketoesters, 1,3-diketone, malonates, and α-cyanoketone with various ring sizes and substitutions, were subjected to the reaction. Remarkably, in all cases high yields and high enantioselectivities were achieved with low catalyst loading (as low as 0.1 mol%) and under mild conditions. The products, such as quaternary α-amino acid derivatives, are versatile building blocks for the synthesis of designer peptides, which could serve as potential therapeutic agents.



Scheme 10.32 Enantioselective α-amination reaction of 1,3-dicarbonyl compounds.

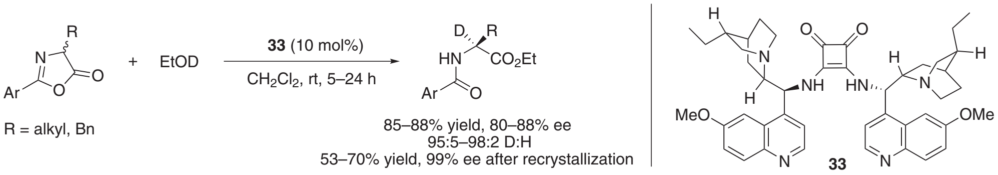
10.3.1.7 **Dynamic Kinetic Resolution and Desymmetrization**

Song and coworkers have developed a series of cinchona-derived dimeric squaramides and have studied their application in dynamic kinetic resolution reaction of racemic azlactones [111]. Using a quinine-derived squaramide catalyst **33**, high enantioselectivities were obtained in a one-pot procedure starting from N-protected racemic amino acids (Scheme 10.33). A broad range of azlactones were suitable substrates for this transformation, affording various natural and non-natural (*S*)-α-amino acid derivatives, while an α-aryl-substituted azlactone (R^1 = Ph, from phenylgycine) gave reduced selectivity (81% ee). Additionally, the catalyst can be recovered by simple precipitation and used for five cycles without loss of selectivity and activity. By switching to a quinidine-derived dimeric catalyst **34**, the corresponding (*R*)-α-amino acid derivatives can be obtained, albeit in slightly reduced enantioselectivity (89–92% ee). Furthermore, the protocol can be applied to the stereoinversion of chiral α-amino acids using optically pure N-protected amino acids as starting materials. The authors pointed out that the monomeric squaramide catalyst **35** provided low enantioselectivity (88% ee for a 0.1 M reaction), and the enantioselectivity was found to decrease noticeably when higher reaction concentrations were applied (84% ee for a 1.0 M reaction). In contrast, the dimeric catalyst provided the same level of selectivity at different reaction concentrations. As with others who had observed such trends, the authors ascribed these phenomena to the high tendency towards self-aggregation for catalyst **35**, while the dimeric catalyst **33** was presumed to not self-associate as a result of the steric hindrance of the two cinchona alkaloid moieties. Further support for the self-association explanation was provided by a DOSY (diffusion ordered spectroscopy) experiment.



Scheme 10.33 Dynamic kinetic resolution of racemic azlactones.

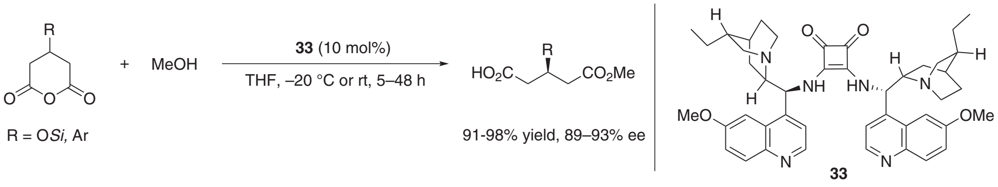
Considering that the α-proton-exchange of racemic azlactones occurred rapidly in the presence of a tertiary amine base, Song and coworkers demonstrated enantioselective synthesis of α-deuterated α-amino acids via dynamic kinetic resolution (DKR) of azlactones with EtOD using cinchona-derived dimeric squaramide catalyst **33** (Scheme 10.34) [112]. The authors noted that by increasing the amount of EtOD, the level of deuterium incorporation increased, whereas the enantioselectivity decreased. By using 50 equivalents of EtOD, the products were obtained with



Scheme 10.34 Enantioselective synthesis of α-deuterated α-amino acids.

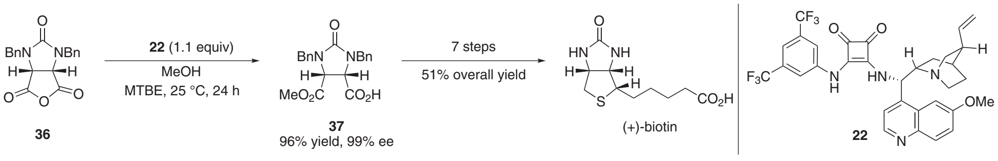
good enantiopurity and >95% deuterium incorporation. For all products, the optical purity can be improved to 99% ee by a single recrystallization. The N-protected amino esters could also be converted into the optically pure α-deuterated α-amino acids upon hydrolysis, without loss of deuterium labeling or optical purity.

Song and coworkers further utilized squaramide **33** for methanolytic desymmetrization of *meso*-glutaric anhydrides (Scheme 10.35) [113, 114]. The authors attributed the high enantioselectivity to the fact that the cinchona-derived dimeric squaramide catalyst does not self-associate. The catalyst can be easily recovered from the reaction mixture after extractive acid/base work up. A thiourea-catalyzed version of this process had been reported by the same authors in 2008 [115].



Scheme 10.35 Desymmetrization of *meso*-glutaric anhydrides catalyzed by squaramide **33**.

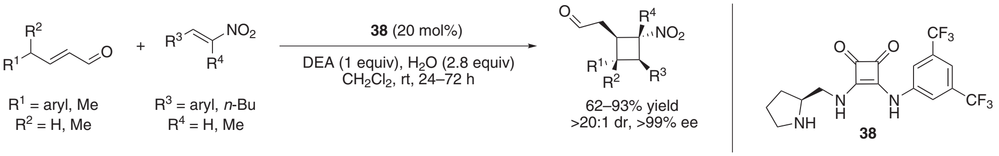
Chen and coworkers have developed a bifunctional quinine-derived squaramide-promoted enantioselective alcoholysis of *meso*-succinic anhydride **36** [116]. Whereas modest enantioselectivity can be obtained in the presence of a catalytic amount of squaramide **22**, high enantioselectivity was realized when more than 1 equivalent of squaramide was utilized (Scheme 10.36). The utility of the squaramide-catalyzed desymmetrization was nicely illustrated by carrying out an efficient synthesis of (+)-biotin from the enantioenriched hemiester **37**, which, in turn, was obtained by desymmetrization of **36**.



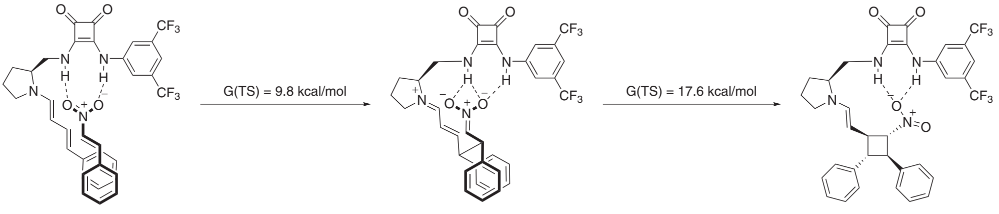
Scheme 10.36 Enantioselective alcoholysis of *meso*-succinic anhydride **36**.

10.3.1.8 **Cascade Reactions**

Recently, Jørgensen and coworkers have developed enantioselective formal [2+2]-cycloadditions via bifunctional hydrogen-bond directed dienamine catalysis [117]. In the presence of squaramide catalyst **38** bearing a chiral secondary amine, the reactions between various γ-substituted-α,β-unsaturated aldehydes and nitroalkenes afforded the [2+2] cycloaddition products in modest to good yields with excellent diastereo- and enantioselectivities (Scheme 10.37). An extensive scope of substrates was studied. Both β-aryl-substituted nitroalkenes bearing electron-withdrawing and electron-donating groups, as well as β-alkyl-substituted nitroalkene, are tolerated. Remarkably, the reaction of an α-methyl-substituted nitroalkene afforded the cyclobutane product containing a quaternary stereocenter. Additionally, γ-aryl-substituted and γ,γ-dimethyl-α,β-unsaturated aldehydes are suitable substrates for this transformation. The catalyst loading can be reduced to 5 mol%, although a longer reaction time is required. The authors proposed that the α,β-unsaturated aldehydes were activated by the amino functionality of the catalyst through dienamine formation, while the nitroalkenes were activated through hydrogen-bond formation with the squaramide moiety of the catalyst. The simultaneous dual activation of the reactants is said to account for the observed stereocontrol in the reaction. Based on computational studies, the authors suggest that the reaction occurs in a stepwise manner (Scheme 10.38). Bond formation between the γ-carbon of the dienamine and the β-carbon of the nitroalkene followed by a rate-limiting bond formation between the β-carbon of the iminium ion and the α-carbon of the nitro group was proposed. This amine-catalyzed formal [2+2]-cycloaddition reaction represents a new approach for the construction of cyclobutanes bearing four contiguous stereocenters.

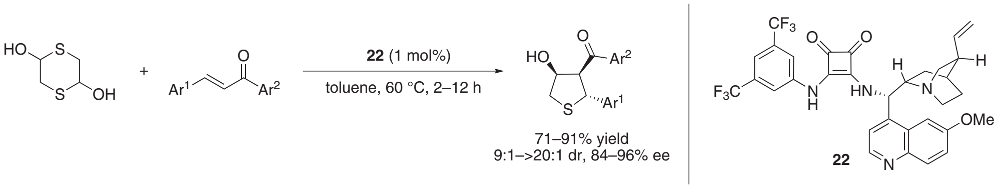


Scheme 10.37 Enantioselective formal [2+2]-cycloadditions catalyzed by squaramide **38**.



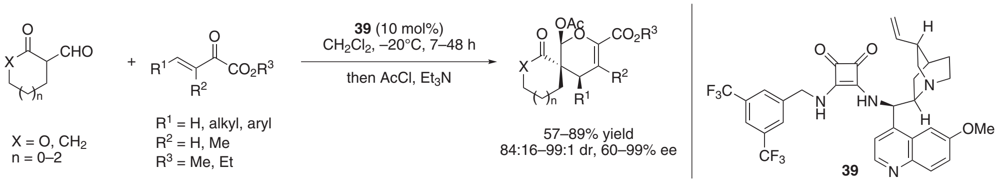
Scheme 10.38 Computational results on the reaction pathway of the formal [2+2]-cycloaddition.

Tetrahydrothiophenes are an important group of sulfur-containing heterocycles. Additionally, some substituted tetrahydrothiophenes have shown interesting biological activities. In a recent report, Xu and coworkers described a squaramide-catalyzed cascade reaction that generates enantioenriched substituted tetrahydrothiophenes [118]. Although low stereoselectivity was obtained in the presence of cinchona alkaloids or bifunctional thiourea catalysts, the quinine-derived squaramide-catalyzed sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol and chalcones proceeded in high diastereo- and enantioselectivity with low catalyst loading (Scheme 10.39). Interestingly, the authors noted that by running the reaction at elevated temperature (60 °C) both the reaction rate and the enantioselectivity were improved. A range of chalcones bearing electron-withdrawing and electron-donating substituents and heteroaromatic rings underwent the squaramide-catalyzed reaction, affording diverse enantioenriched trisubstituted-tetrahydrothiophenes. This transformation represented the first example of non-covalent interaction-mediated cascade reactions of chalcones, and provided facile stereoselective synthesis of trisubstituted tetrahydrothiophenes with three contiguous stereogenic centers.



Scheme 10.39 Enantioselective synthesis of trisubstituted tetrahydrothiophenes.

3,4-Dihydropyrans are versatile synthetic building blocks and define the structural cores for many natural products and pharmaceutical targets. Ma and coworkers developed a squaramide-catalyzed cascade cyclization reaction of β-oxo aldehydes and β,γ-unsaturated α-ketoesters (Scheme 10.40) [119]. High stereoselectivities were achieved using either bifunctional thiourea or squaramide catalysts, and the best results were obtained using the quinidine-derived squaramide **39**. Compared with the author's previous report using $(DHQD)_2PYR$, the squaramide-catalyzed reaction tolerated a broad substrate scope. High diastereoselectivity and modest to high enantioselectivities were achieved using cyclic β-oxoaldehydes with varying ring sizes and substitutions, as well as β,γ-unsaturated α-ketoesters bearing aliphatic or aromatic γ-substituents. Acyclic β-oxoaldehydes also participated in the reaction, yielding the product in high enantioselectivity, albeit with low diastereoselectivity. This Michael addition–hemiacetalization domino sequence is an efficient enantioselective synthesis of spiro-3,4-dihydropyrans bearing three continuous stereocenters, including a quaternary center.



Scheme 10.40 Enantioselective synthesis of spiro-3,4-dihydropyrans.

10.3.2
Summary and Outlook

Although squaramides had been utilized for over 15 years in molecular recognition studies and as hydrogen-bonding spacers in medicinal chemistry, only very recently have their important capabilities as hydrogen-bond donor catalysts been recognized. The highly modular nature of their synthesis has enabled the preparation of a large number of chiral squaramide catalysts, including tertiary amine-squaramides such as cinchona-derived catalysts (**13**, **22**, **24**, and **33**) and cyclohexanediamine-derived catalysts (**17**, **27**, and **32**), secondary amine-squaramides such as proline-derived catalysts (**14** and **38**), and phosphine-squaramate catalyst (**28**). Diverse types of bond-forming processes, including C–C, C–N, C–O, C–P, and C–S bond formation have been achieved through a broad range of squaramide-catalyzed reactions, including Michael addition, Friedel–Crafts reaction, hydrazination reaction, vinylogous aldol reaction, decarboxylative aldol reaction, Morita–Baylis–Hillman reaction, dynamic kinetic resolution, and desymmetrization reactions. Despite the many successes, the precise means through which squaramides impart high enantioselectivities remains to be determined. Various hydrogen-bonding interactions between the squaramide functionality and diverse substrates can be considered to account for the observed stereoselectivities (Figure 10.5). Further computational studies and, especially, structural studies are expected to provide support for the intermediacy of such interactions and thereby shed light on the factors that are important for squaramide's success.

The examples presented in this section have demonstrated the extensive capability of squaramide to function as an effective activation unit for hydrogen-bond donor catalysis. While clearly resembling its well-established urea and thiourea counterparts, squaramide catalysts clearly perform differently in terms of the cata-

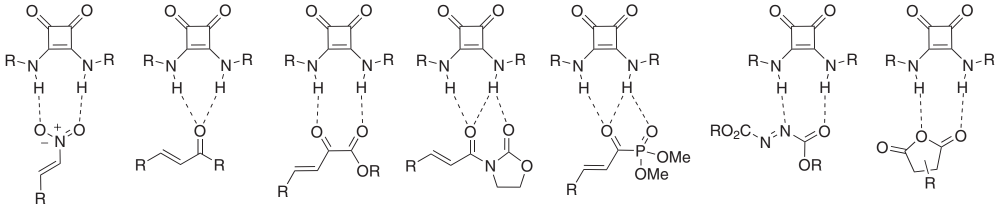


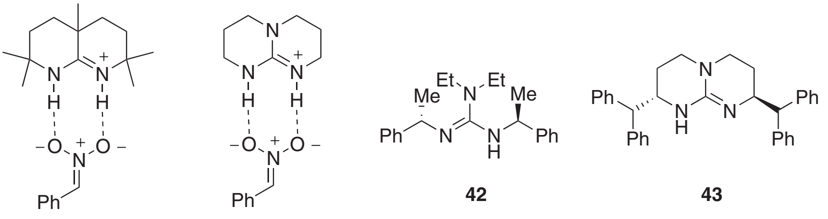
Figure 10.5 Possible binding modes of squaramides to various H-bond acceptors.

lytic activity and selectivity. Squaramides have expanded the range of reactions that can be rendered enantioselective through hydrogen-bond catalysis. Considering the unique double hydrogen-bond donor ability of squaramide functionality, future opportunities for development in squaramide catalysis are immense. For example, the use of squaramide catalysts as monofunctional hydrogen-bond donor catalysts has yet to be developed. While dual mode catalysis based on a combination of squaramide catalysis and other privileged catalytic modes, such as enamine catalysis or nucleophilic catalysis, has been reported, many further opportunities in this subfield remain to be explored. By employing novel types of reactants, new modes of substrate–squaramide interaction patterns could be envisioned and utilized for further reaction development. Squaramide-catalyzed cascade reactions beyond those involving Michael acceptors are conceivable and would provide powerful synthetic methods. Highly stereoselective, squaramide-catalyzed multicomponent reactions have not yet been reported and represent a rich area for further research. The impressive progress made over the last four years confirms the growing importance of squaramide catalysis for asymmetric synthesis. Further investigations of the new directions mentioned above as well as applications to natural product synthesis are expected to lead to the development of even more synthetic methods enabled by squaramide catalysis.

10.4
Guanidines/Guanidiniums

Guanidines and guanidiniums constitute an important catalyst class in the area of metal-free catalysis. Guanidine, as a functional group, owes its early popularity largely to its presence in the amino acid arginine. Additionally, the capability of guanidiniums to form well-defined, hydrogen-bonded, non-covalent complexes with oxyanions such as carboxylates, phosph(on)ates, and sulf(on)ates has been widely utilized in supramolecular chemistry [120, 121].

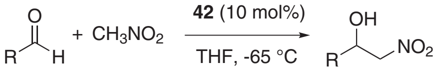
In an important development, in 1992 the Davis and Wynberg groups independently showed using ^{1}H NMR and X-ray crystallographic studies that amidinium (**40**) and guanidinium (**41**) ions bind to the anion of α-nitrotoluene via dual hydrogen bonding (Figure 10.6) [122, 123]. Their studies provide a basis



40 **41** **42** **43**

Figure 10.6 An amidinium and various chiral and achiral guanidines.

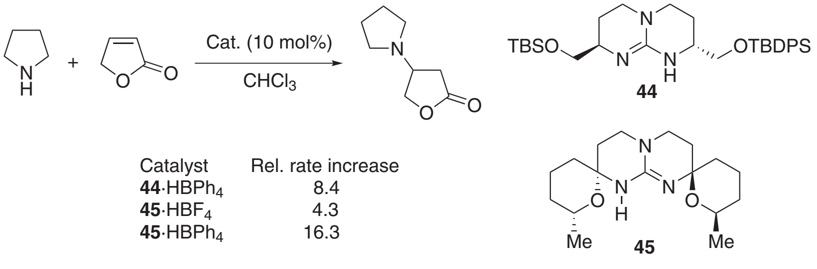
for understanding the many successful enantioselective reactions that have been developed using not only guanidiniums but also thioureas and squaramides. One of the early examples of a chiral guanidine used in a catalytic enantioselective transformation was by Nájera and coworkers in 1994 (Scheme 10.41) [124]. These workers prepared a series of chiral, C_2-symmetric guanidines and tested them as catalysts in the enantioselective Henry reaction of nitromethane with isopentanal and benzaldehyde. Guanidine **42** was found to be the most effective, giving the Henry products up to 54% ee. In 1995, the synthesis of chiral guanidine **43** was reported by Davis and coworkers (Figure 10.6) [125]. Although it was shown to catalyze the conjugate addition of nitroalkanes to methyl vinyl ketone, it did so with low enantioselectivities (9–12% ee).



R = *i*-Bu, 33% yield, 54% ee
R = Ph, 31% yield, 33% ee

Scheme 10.41 Enantioselective Henry reaction catalyzed by guanidine **42**.

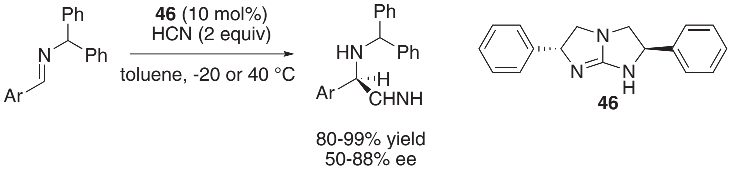
Several guanidinium salts were tested by de Mendoza and coworkers in 1995 as dual hydrogen-bond donors for the activation of α,β-unsaturated lactones in the conjugate addition reaction of pyrrolidine (Scheme 10.42) [126]. The guanidinium salt **44**·$HBPh_4$ was found to have the highest catalytic activity, resulting in a rate enhancement of 8.4 over the uncatalyzed reaction with 10 mol% catalyst loading. Four years later, Murphy and coworkers reported the synthesis of the chiral guanidine **45**, which when used under the same conditions as its $HBPh_4$ salt provided a 16.3-fold rate enhancement (Scheme 10.42) [127]. The authors noted, however, that no asymmetric induction was observed in the reaction.



Catalyst	Rel. rate increase
44·$HBPh_4$	8.4
45·HBF_4	4.3
45·$HBPh_4$	16.3

Scheme 10.42 Guanidinium-catalyzed conjugate addition reactions of pyrrolidine.

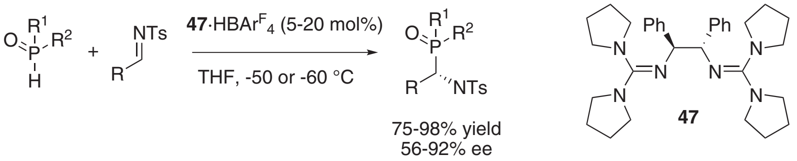
The first highly enantioselective reaction catalyzed by a chiral guanidine was reported by Corey and coworkers in 1999 [128]. C_2-symmetric guanidine **46** was shown to be a highly effective catalyst in the Strecker reaction of aromatic aldimines, affording the Strecker products in high yields and enantioselectivities (Scheme 10.43).



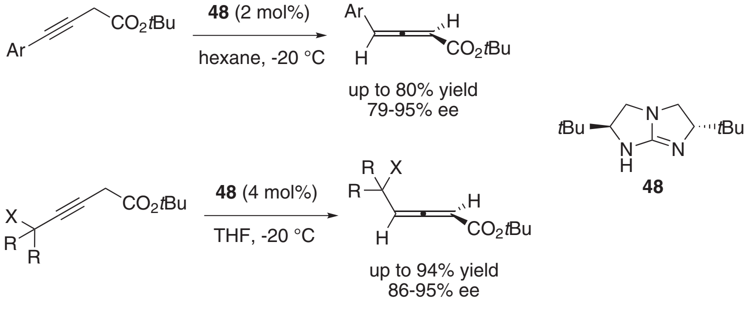
Scheme 10.43 Enantioselective Strecker reaction catalyzed by guanidine **46**.

The developments in the area of enantioselective guanidine and guanidinium catalysis have been reviewed in detail by the Ishikawa, Tan, and Terada groups [129–133]. Moreover, the different mechanisms and modes of activations in guanidine-catalyzed reactions have been reviewed recently by Tan and coworkers [134]. Herein, we will discuss the discoveries in the field since 2009.

The guanidinium salt **47**$\cdot$HBAr$^F{}_4$ was used by Tan and coworkers in the enantioselective phospha-Mannich reaction in 2009 (Scheme 10.44) [135]. An initial screening of the HBF$_4$:**47** ratio showed that a 1 : 1 ratio gave the highest enantioselectivity. Further counter-anion screening revealed **47**$\cdot$HBAr$^F{}_4$ as the most effective catalyst and afforded the phospha-Mannich products in high yields and enantioselectivities. The same research group used guanidine **48** as a Brønsted base catalyst in the enantioselective isomerization of 3-alkynoates to chiral allenoates (Scheme 10.45) [136], the enantioselective allylic addition of *N*-aryl alkylidene-succinimides to imines [137], and the α-amination and Mannich reaction of α-fluorinated aromatic ketones [138].

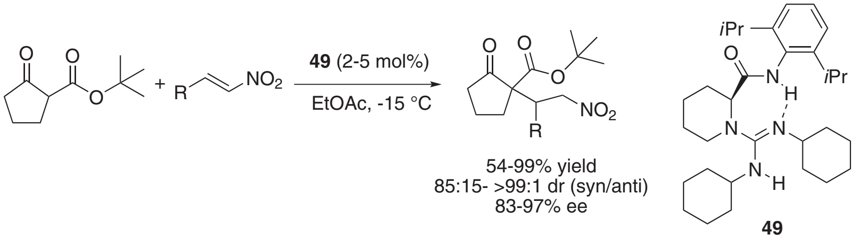


Scheme 10.44 Enantioselective phospha-Mannich reaction.

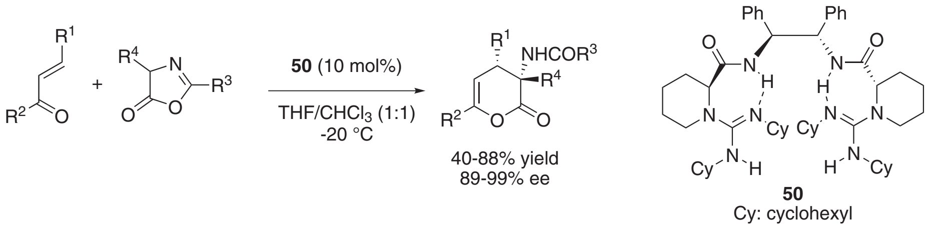


Scheme 10.45 Enantioselective isomerization of 3-alkynoates to chiral allenoates.

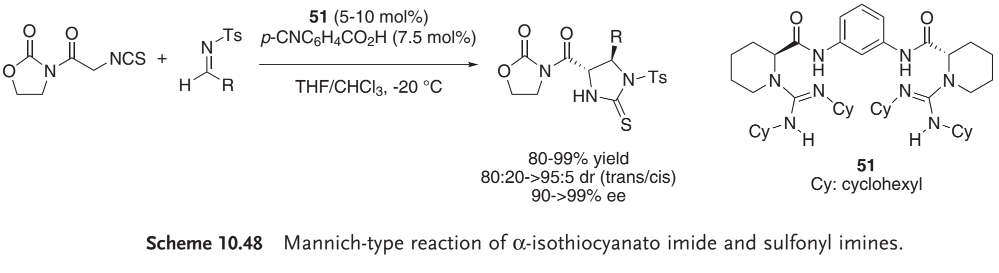
In 2009, Feng and coworkers developed new guanidine catalysts with an amino amide skeleton [139]. Among the various catalysts tested, guanidine **49** was found to be the most active for the enantioselective Michael reaction of a β-ketoester with nitroolefins (Scheme 10.46). The conjugate addition products were obtained in high yields and excellent diastereo- and enantioselectivities. The same researchers used bis-guanidine catalysts for the enantioselective inverse-electron-demand hetero-Diels–Alder reaction of chalcones with azlactones (Scheme 10.47) [140] and enantioselective Mannich-type reaction of α-isothiocyanato imide and sulfonyl imines (Scheme 10.48) [141].



Scheme 10.46 Enantioselective Michael reaction of β-ketoester with nitroolefins.

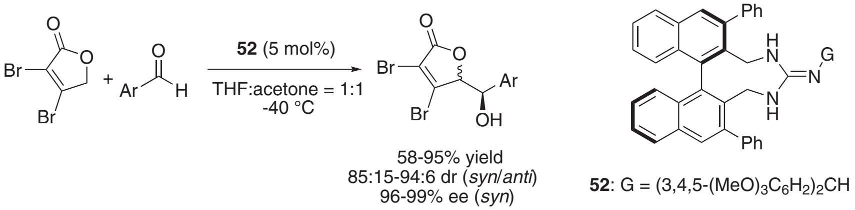


Scheme 10.47 Enantioselective inverse-electron-demand hetero-Diels–Alder reaction of azlactones.



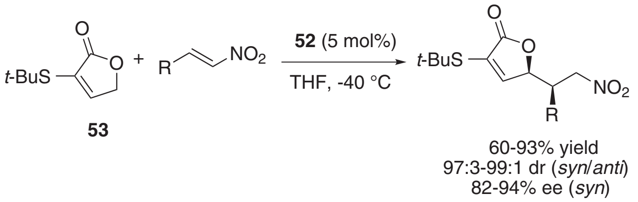
Scheme 10.48 Mannich-type reaction of α-isothiocyanato imide and sulfonyl imines.

Terada and coworkers reported, in 2010, an enantioselective, direct vinylogous aldol reaction of furanone derivatives with aromatic aldehydes catalyzed by axially chiral guanidines (Scheme 10.49) [142]. Initial catalyst screening revealed that both the bulkiness and the electronic nature of the G substituent on the guanidine had a large influence on catalytic activity as well as enantio- and diastereoselectivity. With guanidine **52** in hand, the dichloro-furanone derivative underwent the aldol reaction in high yield (90%) and excellent enantioselectivity (99% ee for *syn*), albeit in lower *syn*/anti ratio (77 : 23). In contrast, when the dibromo-furanone derivative was used, the aldol products were obtained in high yields and high diastereo- and enantioselectivities.

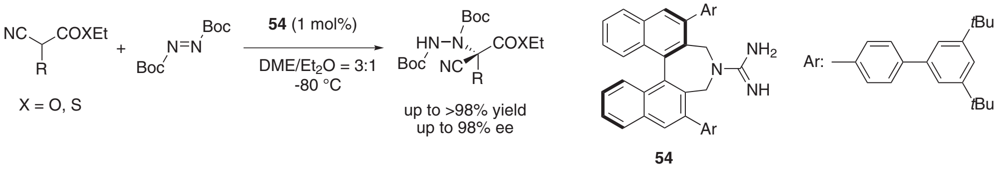


Scheme 10.49 Vinylogous aldol reaction of furanone derivatives with aromatic aldehydes.

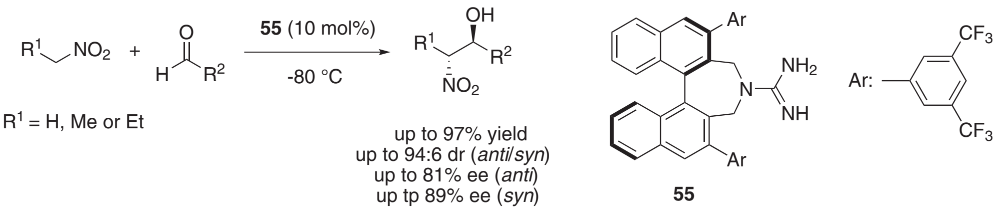
In a related study, the same researchers used guanidine **52** for the enantioselective vinylogous Michael reaction of furanone **53** with various aromatic and aliphatic nitroalkenes (Scheme 10.50) [143]. In addition, several additional asymmetric transformations catalyzed by axially chiral guanidines were reported by Terada and coworkers between 2009–2012 (Schemes 10.51–55) [144–148].



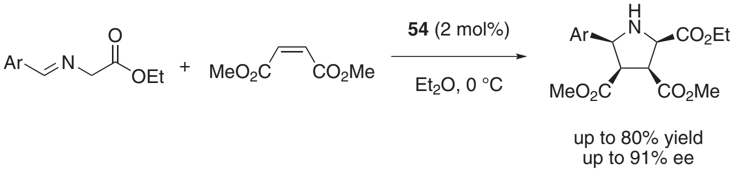
Scheme 10.50 Enantioselective vinylogous Michael reaction of furanone **53**.



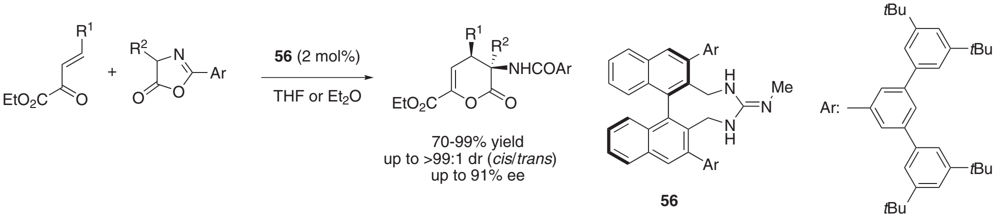
Scheme 10.51 Enantioselective amination of α-cyanothioacetates.



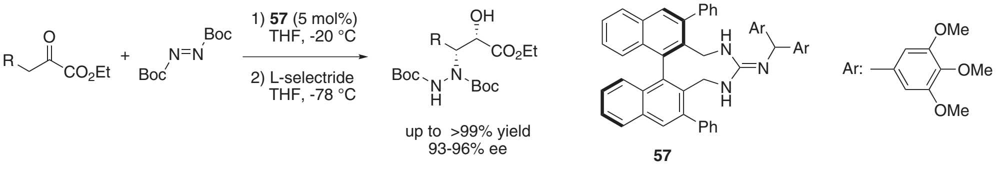
Scheme 10.52 Enantioselective Henry reaction catalyzed by guanidine **55**.



Scheme 10.53 Guanidine-catalyzed enantioselective [3+2] cycloaddition.

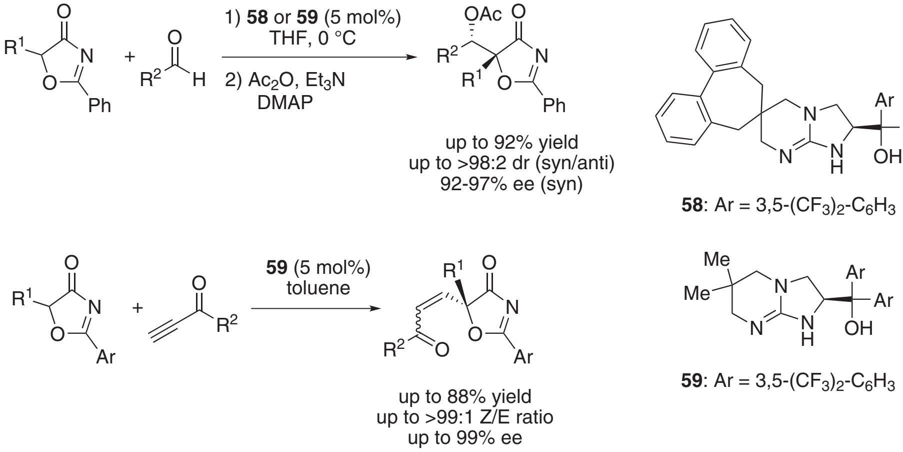


Scheme 10.54 Enantioselective [4+2] cycloaddition of azlactones catalyzed by **56**.



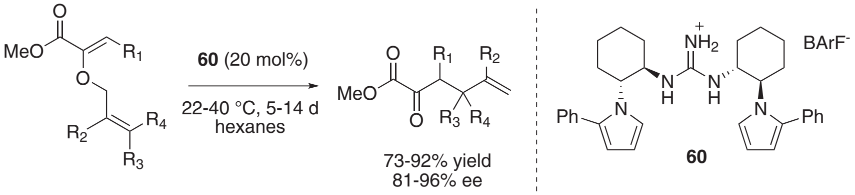
Scheme 10.55 Guanidine-catalyzed enantioselective amination of α-ketoesters.

In 2010, Misaki, Sugimura, and coworkers used the chiral guanidines **58** and **59** for the enantioselective aldol reaction of 5*H*-oxazol-4-ones with aliphatic aldehydes (Scheme 10.56) [149]. The aldol products were obtained in high *syn*/anti ratios and excellent enantioselectivities. In addition, the authors showed that these products could be converted into the corresponding α,β-dihydroxycarboxylic amides or esters. Guanidine **59** was also found to be a highly effective catalyst for the conjugate addition reaction of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds [150]. High *Z*/*E* ratios and enantioselectivities were obtained over a wide range of substrates.



Scheme 10.56 Enantioselective aldol and Michael reactions of 5*H*-oxazol-4-ones.

Jacobsen and coworkers reported in 2008 a highly effective enantioselective Claisen rearrangement of ester-substituted allyl vinyl ethers catalyzed by the guanidinium salt **60** (Scheme 10.57) [151]. The reactions took place under mild conditions (22–40 °C), affording the rearrangement products up to 96% ee, albeit with long reaction times (5–14 days). This methodology was extended to the enantioselective Claisen rearrangements of *O*-allyl β-ketoesters, giving rise to the formation of quaternary center-containing β-ketoesters [152]. A detailed investigation of the mode of action of this catalyst, including computational and solution studies, has been disclosed recently [153].

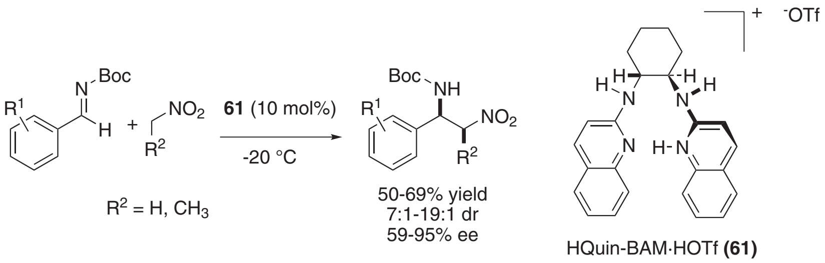


Scheme 10.57 Enantioselective Claisen rearrangement catalyzed by guanidinium salt **60**.

10.5
Miscellaneous Brønsted Acids

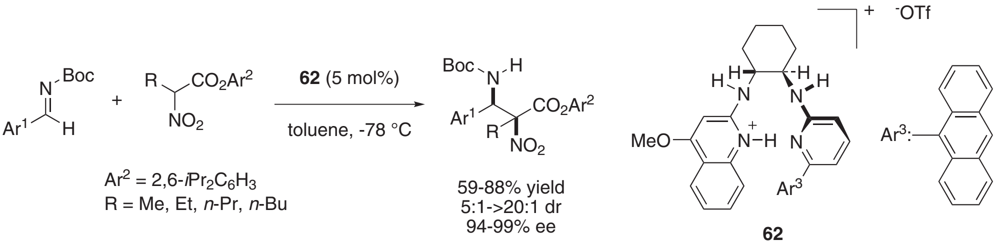
10.5.1
Aminopyridiniums

Johnston and coworkers reported in 2004 an enantioselective aza-Henry reaction of nitroalkanes with Boc-protected imines catalyzed by the mono-protonated chiral bis-amidine salt **61** (Scheme 10.58) [154]. This catalyst class was also found to be

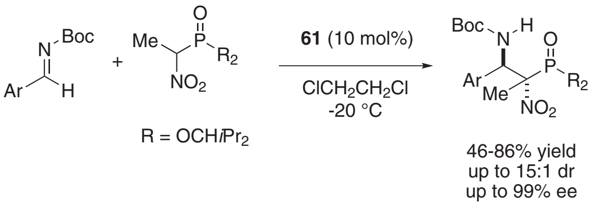


Scheme 10.58 Enantioselective aza-Henry reaction catalyzed by **61**.

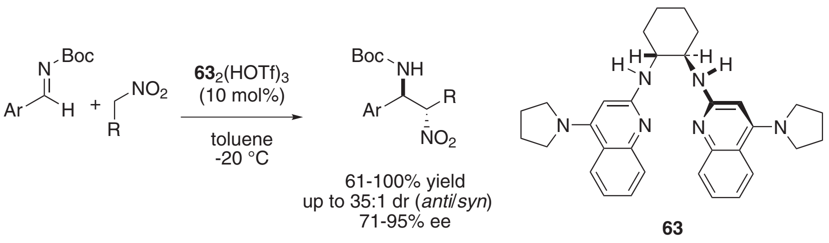
highly effective in the enantioselective addition of nitroacetic acid derivatives (Scheme 10.59) [155–157] and α-nitrophosphonates (Scheme 10.60) [158] as well as other nitroalkanes (Scheme 10.61) [159, 160] to *N*-protected imines. The pK_a values of various Brønsted acids used by Johnston were determined using an NMR titration method [161].



Scheme 10.59 Enantioselective addition of α-nitroesters to *N*-Boc imines.

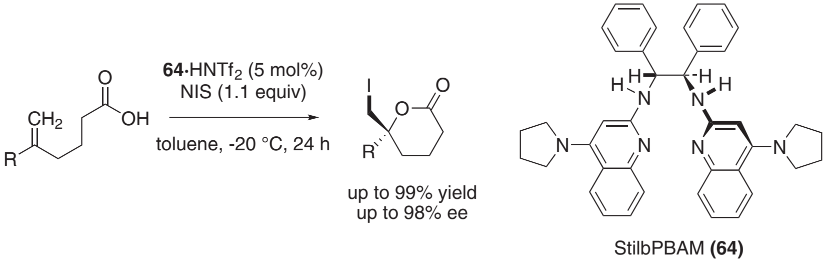


Scheme 10.60 Enantioselective addition of α-nitrophosphonates to *N*-Boc imines.



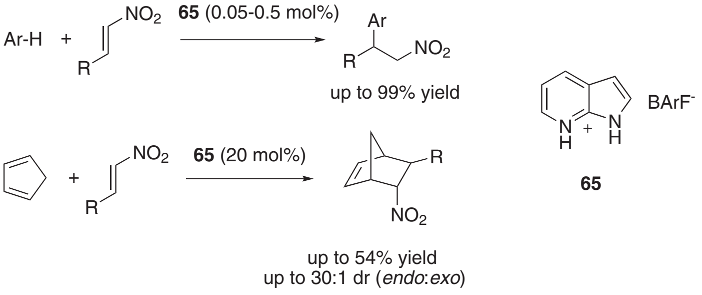
Scheme 10.61 Enantioselective addition of nitroalkanes to *N*-Boc imines.

Recently, Johnston and coworkers reported an impressive application of catalysis by the amidinium salts in an enantioselective iodolactonization reaction (Scheme 10.62) [162]. While the free bases were effective in catalyzing the reaction, higher enantioselectivities were obtained with the mono-protonated salts. Additionally, the authors discovered a high dependence of enantioselectivity on the nature of the achiral counter-ion, and among the anions tested the triflimidate anion was found to be the best in terms of both yield and enantioselection. With 5 mol% of the catalyst **64** · $HNTf_2$, the iodolactonization products were obtained in high yields (up to 99%) and excellent enantioselectivities (up to 98% ee).

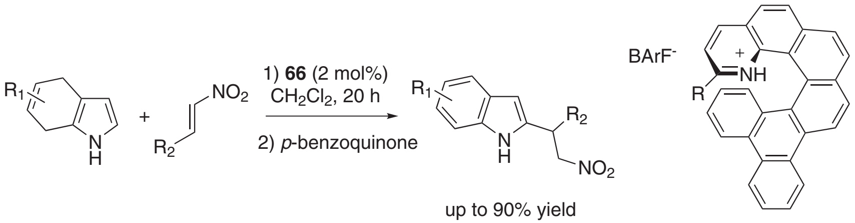


Scheme 10.62 Enantioselective iodolactonization reaction.

Takenaka and coworkers used 2-aminopyridinium salts as dual hydrogen-bond donors for the activation of nitroalkenes. The 7-azaindolium salt **65** was found to be particularly effective for the Friedel–Crafts reaction of nitroalkenes with various electron-rich arenes as well as for intra- and intermolecular Diels–Alder reactions (Scheme 10.63) [163, 164]. The same concept was successfully applied to the enantioselective conjugate addition of 4,7-dihydroindoles to nitroalkenes using helical chiral 2-aminopyridinium salts (Scheme 10.64) [165]. The reaction was found to have a broad substrate scope, affording various 2-substituted indoles in good to high enantiomeric ratios.



Scheme 10.63 Activation of nitroalkenes by the 7-azaindolium salt **65**.

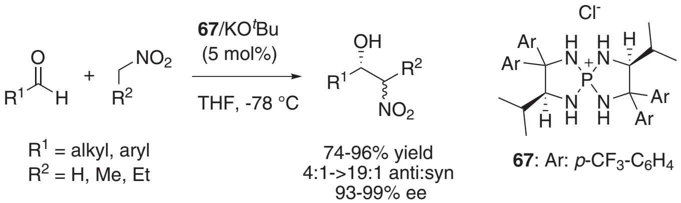


66: R= 1-adHN-
ad = adamantyl

Scheme 10.64 Enantioselective conjugate addition of 4,7-dihydroindoles to nitroalkenes.

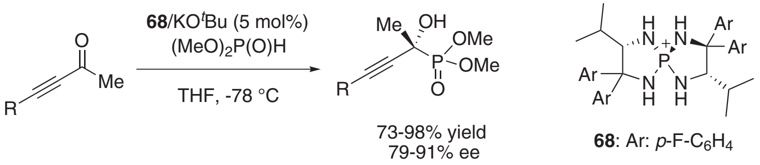
10.5.2
Tetraaminophosphoniums

In 2007, Ooi and coworkers introduced chiral tetraaminophosphonium salts as a new class of Brønsted acids [166]. Similar to the guanidine/guanidinium case, these tetraaminophosphonium salts act as Brønsted bases in their neutral/deprotonated (triaminoiminophosphorane) form, while they can also be used as mono-functional Brønsted acids in their protonated, phosphonium form. Phosphonium salt **67**, when neutralized *in situ* with KO^{t}Bu, was shown to be a highly effective catalyst in the enantioselective Henry reaction of nitroalkanes with various aromatic and aliphatic aldehydes (Scheme 10.65). The same strategy was further applied to the catalytic asymmetric Henry reaction of ynals [167] and hydrophosphonylation of ynones (Scheme 10.66) [168]. Bifunctional catalysis using this scaffold were also obtained using the carboxylate salts of tetraaminophosphoniums in the direct Mannich reaction of sulfonyl imines with azlactones (Scheme 10.67) [169].



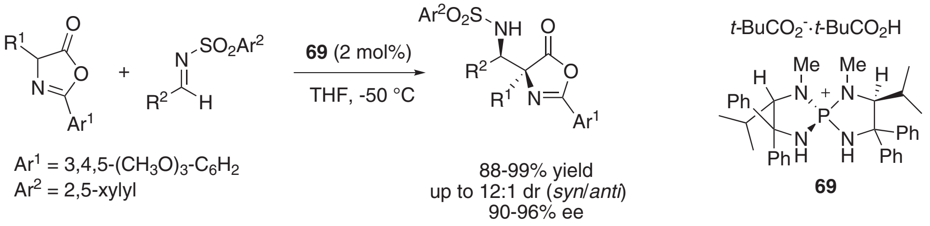
67: Ar: *p*-CF_3-C_6H_4

Scheme 10.65 Enantioselective Henry reaction of nitroalkanes with aldehydes.



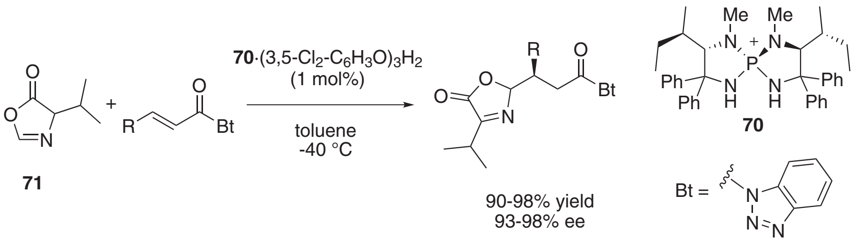
68: Ar: *p*-F-C_6H_4

Scheme 10.66 Enantioselective hydrophosphonylation of ynones.

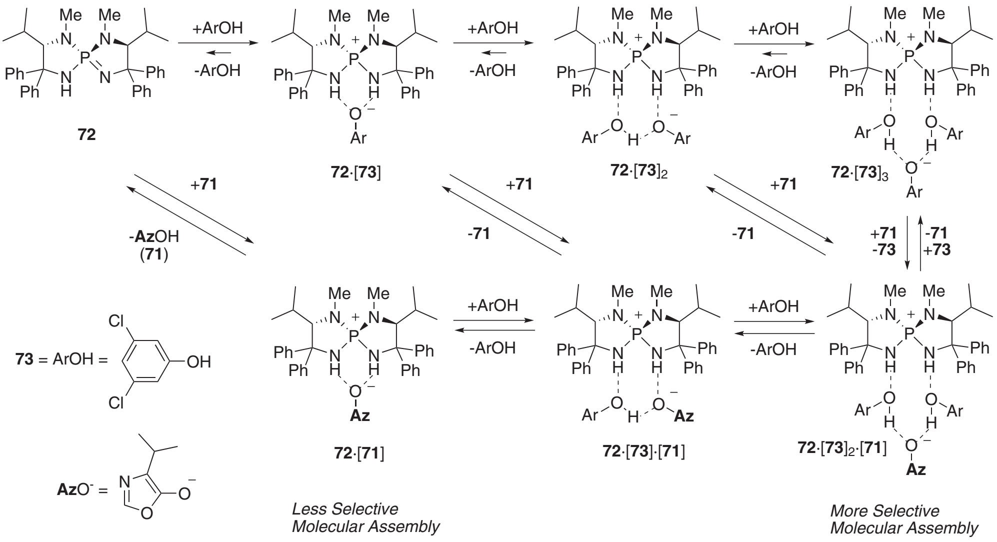


Scheme 10.67 Enantioselective Mannich reaction of sulfonyl imines with azlactones.

This concept was improved further by Ooi and coworkers as the supramolecular catalyst system **70**·$(3,5\text{-}Cl_2\text{-}C_6H_3O)_3H_2$ was discovered to be highly effective in the conjugate addition of azlactone **71** to α,β-unsaturated acylbenzotriazoles (Scheme 10.68) [170, 171]. Low-temperature ^{31}P NMR studies revealed that phosphorane **72** selectively gave the H-bonded complexes **72**·[**73**], **72**·[**73**]$_2$, and **72**·[**73**]$_3$ when treated with the corresponding amounts of phenol **73** (Scheme 10.69) [172]. The structures of these complexes were further verified by X-ray crystallographic analysis. In addition, when **72** and **72**·**[73]** were used as catalysts, low ee values were obtained (51 and 67% ee, respectively) whereas complexes **72**·[**73**]$_2$ and **72**·[**73**]$_3$ gave almost the same, high enantioselectivity (89 and 90% ee). In light of these observations, the authors proposed that the complexes **72**·[**73**]$_n$ (n = 0–3) could deprotonate the azlactone **71** to give the corresponding, reactive intermediates **72**·[**73**]$_n$[**71**] in which enantioselectivity increases as n increases. Moreover, **72**·[**73**]$_2$ and **72**·[**73**]$_3$ are expected to give the same complex, **72**·[**73**]$_2$[**71**], upon reaction with the azlactone **71**, which explains why similar enantiomeric excesses were obtained when these complexes were used.

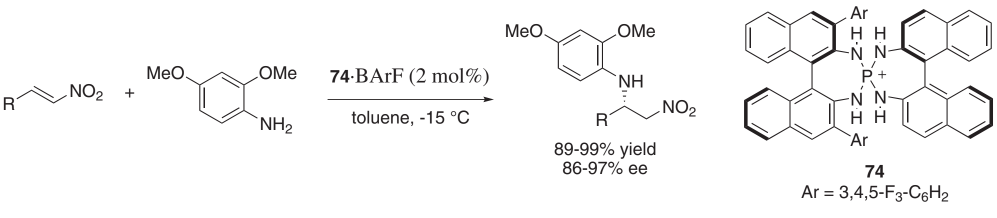


Scheme 10.68 Conjugate addition of azlactone **71** to α,β-unsaturated acylbenzotriazoles.



Scheme 10.69 Proposed molecular assemblies for Ooi's catalyst.

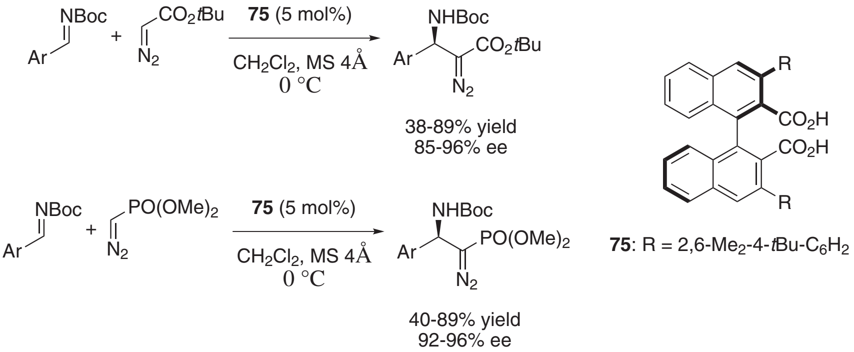
The latter mode of activation, in which a charged tetraaminophosphonium salt acts as a Brønsted acid, was realized by the same research group in 2009. Enantioselective aza-Michael reaction of 2,4-dimethoxyaniline with nitroalkenes afforded the conjugate addition products in excellent yields and high enantiomeric excesses (Scheme 10.70) [173, 174]. Similarly, chiral diaminooxaphosphonium salts have been used as Brønsted acids in the asymmetric protonation reactions of ketene disilyl acetals [175].



Scheme 10.70 Aza-Michael reaction of 2,4-dimethoxyaniline with nitroalkenes.

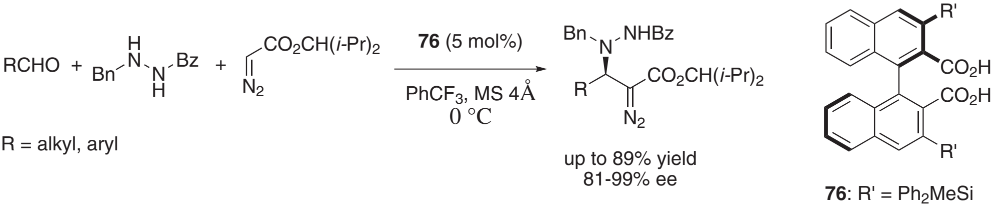
10.5.3
Axially Chiral Dicarboxylic Acids

Axially chiral dicarboxylic acids were introduced by Maruoka and coworkers as a new class of Brønsted acid catalysts in 2007 [176]. The enantioselective Mannich reaction of aromatic *N*-Boc imines and diazo compounds catalyzed by the dicarboxylic acid **75** afforded the Mannich adducts in good to high yields and high enantioselectivities (Scheme 10.71). In a recent full account of this study, the methodology was further extended to the Mannich reaction of aromatic *N*-Boc imines with tolyl (diazomethyl)sulfone [177]. In addition, the X-ray crystal structure of a 1 : 1 co-crystal of **75** and 4-pyrrolidinopyridine revealed an intramolecular hydrogen bond between the two carboxylic acids while the second carboxylic acid is in the carboxylate form and makes an intermolecular H-bond to the protonated pyridinium.

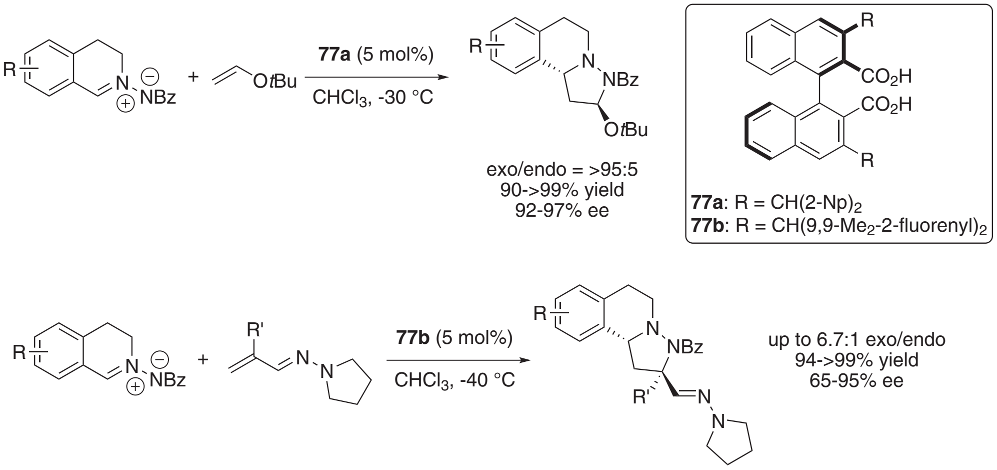


Scheme 10.71 Enantioselective Mannich reaction catalyzed by dicarboxylic acid **75**.

Further applications of this catalyst class as Brønsted acids were shown by Maruoka and coworkers in various enantioselective reactions, such as addition of aza-enamines and vinylogous aza-enamines to imines [178, 179], addition of diazo compounds to *in situ* generated acyclic azomethine imines (Scheme 10.72) [180], and 1,3-dipolar cycloaddition reactions of cyclic azomethine imines with enol ethers and vinylogous aza-enamines (Scheme 10.73) [181].



Scheme 10.72 Addition of diazo compounds to *in situ* generated acyclic azomethine imines.



Scheme 10.73 Enantioselective 1,3-dipolar cycloaddition reactions of azomethine imines.

10.5.4
Stronger Brønsted Acids

As mentioned earlier, a review of key developments in the use of chiral phosphoric acids will be provided by Professor Akiyama in the Chapter 11. It is also worth noting that recent years have seen the development of other strong Brønsted acids with the binaphthalene backbone, such as those by the Yamamoto [182–185], List [186–189], and Toste groups [190].

10.6
Addendum

After the manuscript of this chapter was written, several reports were published on the catalysis of various transformations using chiral alcohols and silanols [191, 192], squaramides [193–197], guanidines [198–201], amidiniums [202], iminophosphoranes and triazoliums [203–205], dicarboxylic acids [206], and other strong Brønsted acids [207, 208].

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11

Brønsted Acids: Chiral Phosphoric Acid Catalysts in Asymmetric Synthesis

Keiji Mori and Takahiko Akiyama

11.1

Introduction

The origin of "chiral Brønsted acid catalysts" [1] can be traced to catalysts that act as a hydrogen bond catalyst. Jacobsen and coworkers reported the enantioselective Strecker reaction by means of peptide-based thiourea catalysts [2]. In 2003, Rawal and coworkers reported the enantioselective hetero-Diels–Alder reaction catalyzed by TADDOL, which could be easily prepared from tartaric acid [3]. In contrast to neutral chiral Brønsted acid catalysts that function as hydrogen bond donor catalysts, Akiyama *et al*. [4] and Uraguchi and Terada [5] independently developed chiral phosphoric acid diester **1** with the BINOL backbone as a stronger chiral Brønsted acid catalyst in 2004. After the emergence of those two reports, chiral phosphoric acid became well known as an excellent chiral Brønsted acid catalyst, attracting the attention of synthetic organic chemists. Various enantioselective reactions were reported thereafter. This chapter deals with recent achievements in the development of enantioselective transformations using axially chiral phosphoric acid catalysts **1** (Figure 11.1).

11.1.1

Design of Chiral Phosphoric Acids

We envisaged that the phosphoric acid moiety is an ideal component for the development of the chiral Brønsted acid (Figure 11.2) for the reasons cited below:

1) Phosphoric acid derivatives easily form a cyclic system, thereby securing the rigidity of the asymmetric environment of the chiral backbone.
2) Phosphoryl oxygen functions as a Lewis basic site and hence works as an acid/base dual functional catalyst.
3) Various substituents (X) can be introduced at the 3,3′-positions of the chiral backbone, effectively providing the requisite chiral environment for highly enantioselective induction.

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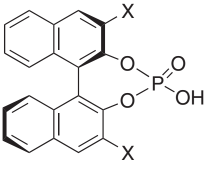


(*R*)-**1**

Figure 11.1 Chiral phosphoric acid catalyst.

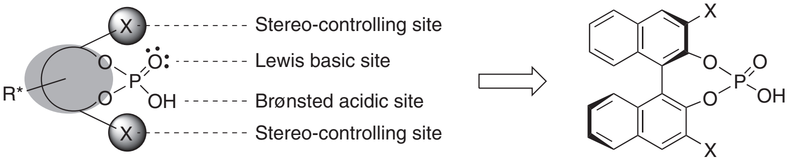
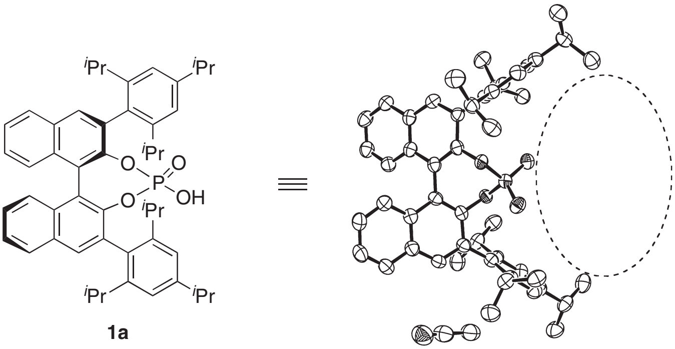


Figure 11.2 Design of chiral Brønsted acid catalyst.



1a

Figure 11.3 X-Ray structure of TRIP·MeCN·0.5H_2O. Hydrogen atoms are omitted for clarity.

4) The moderate acidity [cf. pK_a of $(EtO)_2P(O)OH = 1.3$] suppresses the strong dissociation of proton (H^+) and the chiral anion moiety, which is an important factor for the development of a chiral Brønsted acid.

Generally, the most important consideration in the design of a novel chiral catalyst is the selection of a chiral source (backbone). Akiyama's and Terada's groups independently employed axially chiral biaryls, particularly BINOL derivatives, as the chiral source for the construction of ring structures, because the C_2-binaphthyl backbone, such as BINAP, has been utilized as a chiral ligand for metal-catalyzed asymmetric reactions and is well recognized as a reliable chiral scaffold. This *C*2-symmetry is crucial for phosphoric acid derivatives because the same catalyst molecule is generated when the acidic proton migrates to the phosphoryl oxygen. In addition, both enantiomers of BINOL derivatives are commercially available. Most importantly, various substituents (X) can be easily introduced to the 3,3′-positions of the binaphthyl backbone, enabling control of the steric and electronic properties of the asymmetric environment of the catalyst. Figure 11.3 illustrates the X-ray structure of phosphoric acid with 2,4,6-triisopropylphenyl (TRIP) groups **1a** reported by List and coworkers [6]. Clearly, the BINOL backbone and the 2,4,6-triisopropyl groups at the 3,3′-positions offer the appropriate cavity for the asymmetric induction.

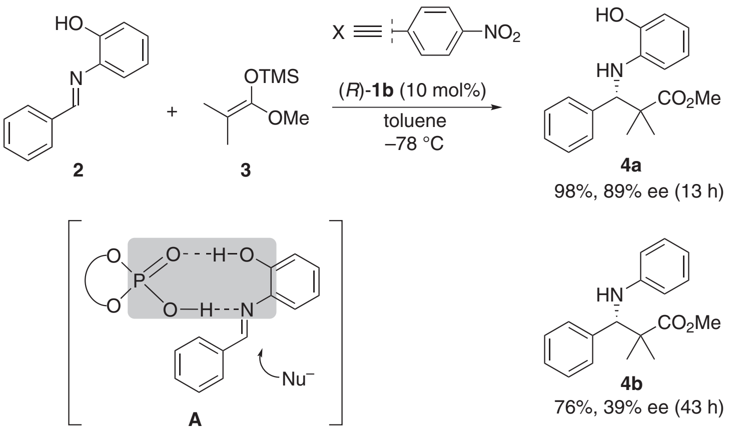
11.2
Reaction with Imines

Because imine has a basic nitrogen atom, a Brønsted acid turned out to be effective as the activator of imines. The seminal work of Akiyama and Terada in 2004 paved the way for chiral Brønsted acid catalysis in nucleophilic addition to imines.

11.2.1
Mannich Reaction

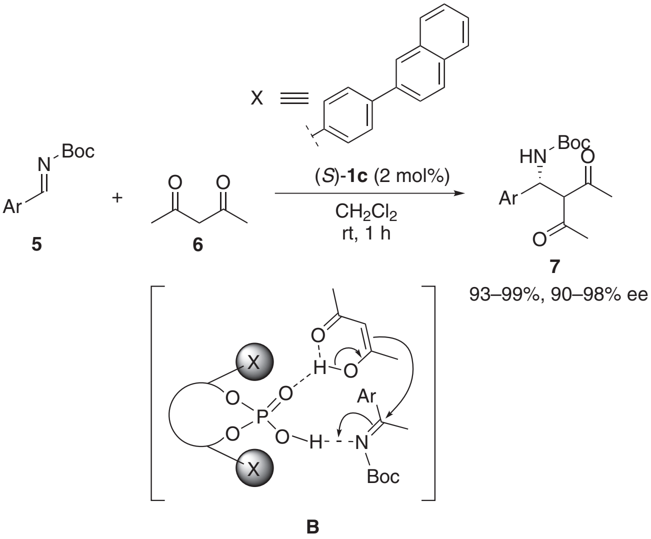
Enantioselective Mannich reactions are widely used for the construction of optically active β-amino carbonyl compounds that serve as versatile intermediates for the synthesis of biologically active compounds [7].

In 2004, Akiyama *et al.* reported that the Mannich reaction of ketene silyl acetal with aldimine derived from 2-hydroxyaniline in the presence of **1b** afforded amine **4a** in 98% yield with 89% ee (Scheme 11.1) [4]. The key point of this transformation resides in the 2-hydroxyphenyl portion of the aldimine. The aldimine without the hydroxy group, from aniline, significantly lowered the enantioselectivity to 39%. A detailed calculation of the transition state model of this reaction revealed that the two hydrogen bonds between the catalyst and the 2-hydroxyphenyl portion of aldimine were crucial for the high enantioselectivity. The nine-membered ring transition state model A derived from the hydrogen bond network gave sufficient rigidity, resulting in the excellent enantioselectivity [8].



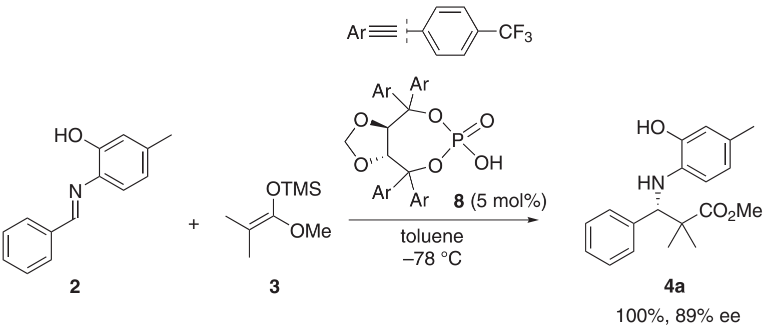
Scheme 11.1 Enantioselective Mannich-type reaction.

In almost the same period, Uraguchi and Terada reported the direct Mannich reaction of *N*-Boc-protected imines with acetyl acetone (Scheme 11.2) [5]. In their direct Mannich reaction, phosphoric acid also worked as a dual functional catalyst: the Brønsted acidic moiety of phosphoric acid catalyst **1c** activated aldimines **5**, and the Lewis basic site (phosphoryl oxygen) interacted with the O–H proton of the enol form of **6**. As a result, the reaction proceeded under a chiral environment created by phosphoric acid **1**, acetyl acetone, and aldimine through hydrogen-bonding interactions to furnish optically active products **7**.



Scheme 11.2 Enantioselective direct Mannich reaction.

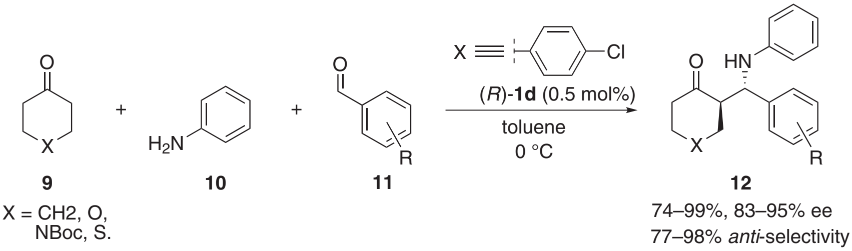
Chiral phosphoric acids are not restricted to those originating from BINOL. TADDOL-based phosphoric acid **8** was developed by Akiyama *et al.* and applied to the Mannich-type reaction (Scheme 11.3) [9]. Interestingly, the aryl substituents



Scheme 11.3 Enantioselective Mannich-type reaction catalyzed by TADDOL-based phosphoric acid.

of TADDOL strongly affected both the chemical yield and the enantioselectivity. Use of the 4-$CF_3C_6H_4$ group on the TADDOL moiety was essential.

Gong and coworkers applied chiral phosphoric acid to the three-component direct Mannich reaction. The one-pot reaction of ketones **9**, aniline (**10**), and aromatic aldehydes **11** proceeded smoothly by means of 0.5 mol% **1d** to give the desired Mannich adducts **12** in good yields with high enantio- and *anti*-selectivities (Scheme 11.4) [10]. They also showed the coupling reaction of acyclic ketones, such as acetone and acetophenone. Although increased catalyst loading (5 mol%) was required, the desired Mannich adducts were obtained in good yields with good enantioselectivities (70–86% ee).



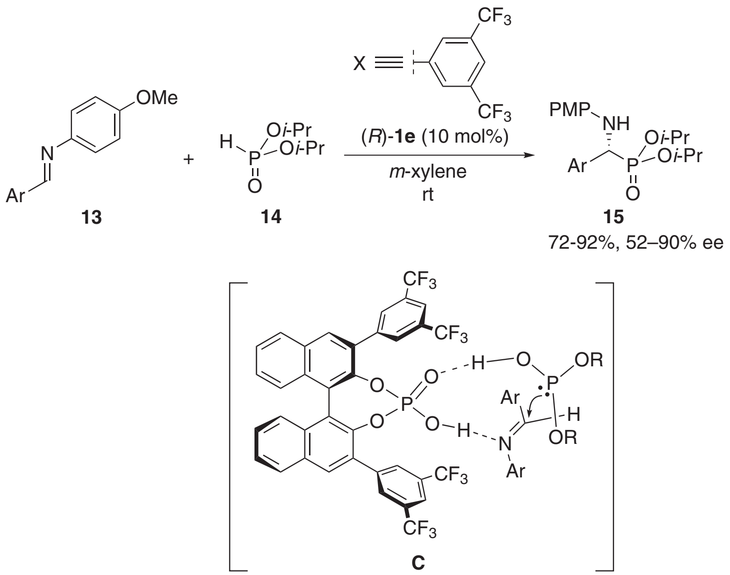
Scheme 11.4 Enantioselective three-component Mannich reaction.

Rueping *et al.* reported achiral Brønsted acid assisted chiral Brønsted acid catalysis in the direct Mannich reaction of acyclic ketones. The reaction of *N*-aryl imines with acetophenone was conducted using a chiral phosphoric acid in the presence of acetic acid as the co-catalyst and the resulting products were obtained in moderate yields [11].

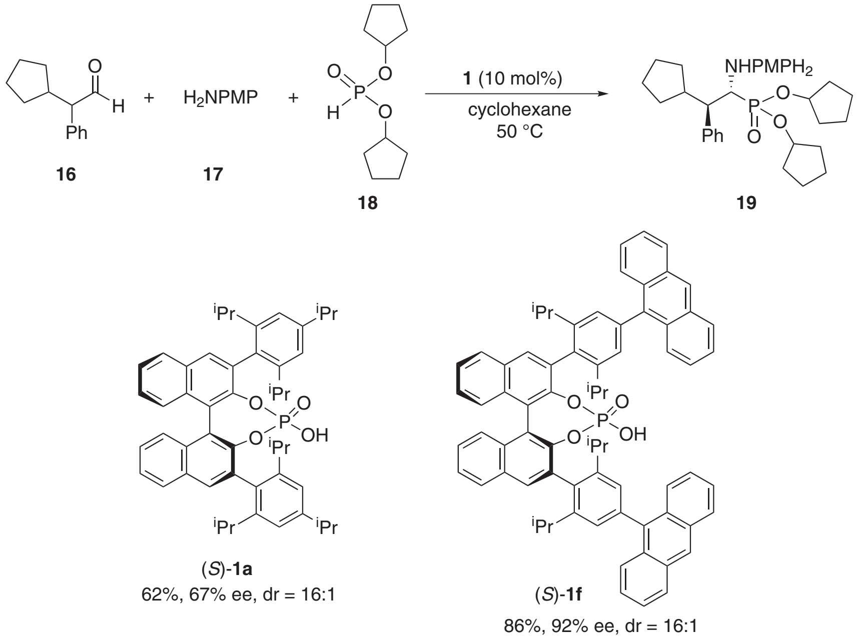
11.2.2
Hydrophosphonylation

The hydrophosphonylation of aldimines **13** with dialkyl phosphite **14** was catalyzed by **1e** to give α-amino phosphonates **15** (Scheme 11.5), which are attractive mimics of α-amino acids, with good to high enantioselectivities. In this case, the use of aldimines derived from *p*-anisidine gave the best result [12]. Interestingly, the 2-hydroxyphenyl group on the nitrogen of aldimine had a detrimental effect on the stereoselectivity of this transformation because the coordination of phosphoryl oxygen to the hydroxy group of the phosphite played an important role in this reaction, as shown in transition state model C.

List and coworkers reported the three-component reaction of aldehyde **16**, *p*-anisidine (**17**), and di(3-pentyl)phosphite **18**, namely, the Kabachnik–Fields reaction, by means of chiral phosphoric acid (Scheme 11.6) [13]. An important feature of this reaction is that catalyst **1f** with a bulky substituent (9-anthryl group) at the *para*-position of the 2,6-diisopropylphenyl group had a significant effect on the enantioselectivity. The desired product **19** was obtained in 86% yield with excellent



Scheme 11.5 Enantioselective hydrophosphonylation reaction.

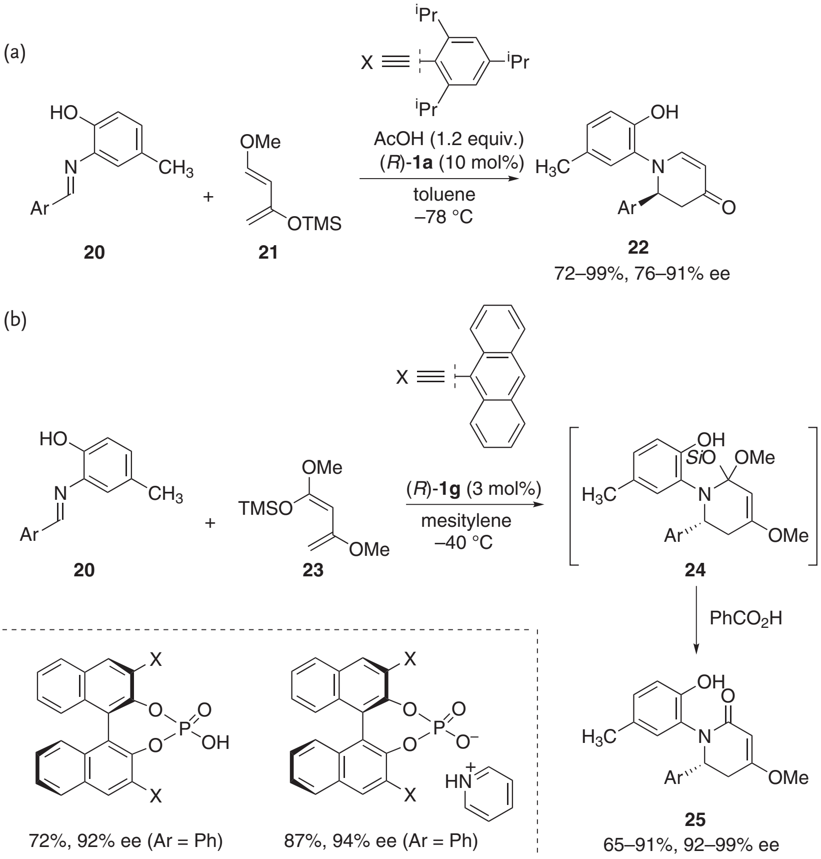


Scheme 11.6 Enantioselective Kabachnik–Fields reaction.

enantio- and *anti*-selectivities (92% ee), although the selectivity was decreased to 67% ee when simple TRIP catalyst **1a** was used.

11.2.3
Cycloaddition Reaction

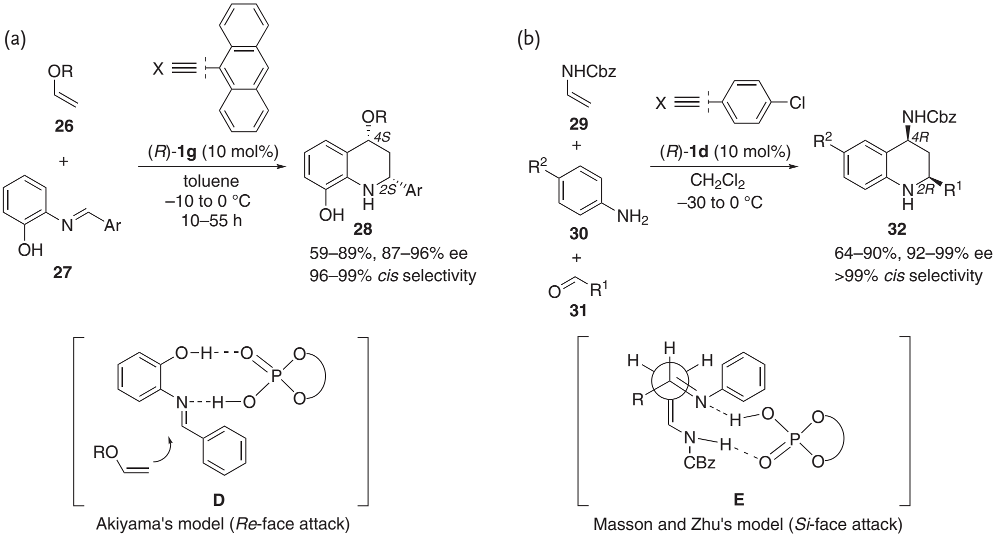
The enantioselective hetero-Diels–Alder reaction of siloxydienes, such as Danishefsky's and Brassard's dienes, with imines provides an efficient route for the preparation of functionalized nitrogen-containing heterocycles in optically active forms. Akiyama and coworkers reported the first catalytic enantioselective hetero-Diels–Alder reaction of Danishefsky's diene (**21**) with aromatic imines **20** using chiral phosphoric acid catalyst **1a** (Scheme 11.7a) [14]. The desired dihydropyridinones **22** were obtained in good yields with high enantioselectivities. Notably, the addition of an equimolar amount of acetic acid was effective in improving the enantioselectivity. Akiyama and coworkers also reported an enantioselective



Scheme 11.7 Enantioselective hetero-Diels–Alder reaction catalyzed by **1**.

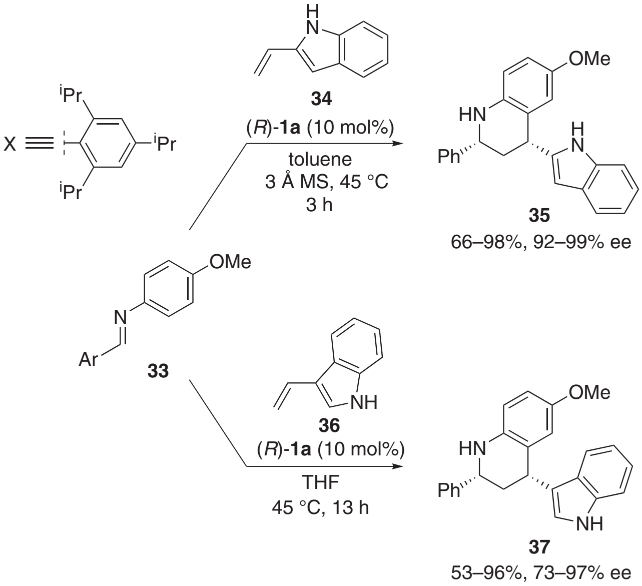
hetero-Diels–Alder reaction of Brassard's diene (**23**) with imines (Scheme 11.7b). However, one of the problems associated with Brassard's diene is its instability under acidic conditions. They were able to overcome this problem by employing the pyridinium salt of phosphoric acid catalyst **1g**, which has weaker Brønsted acidity than phosphoric acid itself. Both chemical yield and enantioselectivity were improved to 87% and 94%, respectively (72% yield and 92% ee with **1g**) [15].

Akiyama and coworkers also reported the enantioselective inverse electron demand Diels–Alder reaction, namely, the Povarov reaction (Scheme 11.8a). They developed a highly enantioselective reaction of *N*-aryl imines **27** with vinyl ethers **26** using chiral phosphoric acid **1g** [16]. Masson, Zhu, and coworkers applied the three-component coupling process to the enantioselective Povarov reaction using enecarbamates **29** instead of vinyl ethers **26** as electron-rich alkenes (Scheme 11.8b) [17]. Interestingly, the absolute stereochemistry of the resulting product **32** was different from that of Akiyama's method even when the (*R*)-BINOL derived phosphoric acid was used in both cases. Although the vinyl ethers afforded (2*S*,4*S*)-quinoline derivatives **28**, the (2*R*,4*R*)-enantiomers were the major products in the case of enecarbamates. One possible explanation for this inverse stereochemical outcome is the difference in the hydrogen-bonding mode. In Akiyama's catalytic system, the phosphoric acid activated only the electrophile via participation of the *o*-hydroxy group. The *Re*-face attack by the vinyl ether on the imine via transition state D would afford the (2*S*,4*S*) stereoisomer. In contrast, the phosphoric acid acted as a bifunctional catalyst that activated both the nucleophile and the electrophile via transition state E to allow a pseudo-intramolecular *Si*-face attack by enecarbamate **29** on the imine in the latter case.



Scheme 11.8 Enantioselective inverse electron demand hetero-Diels–Alder reaction catalyzed by **1**.

Vinylindole derivatives (**34** and **36**) are also good candidates for the Povarov reaction because of their peculiar reactivity as electron-rich alkenes [18]. Bernardi, Ricci, and coworkers successfully demonstrated the enantioselective Povarov reaction of *N*-aryl imines **33** with 2-vinylindole (**34**) and 3-vinylindole (**36**) (Scheme 11.9). Phosphoric acid catalyst **1a** acted as an efficient catalyst for the reaction of **34** with various imines, affording the corresponding indole-substituted tetrahydroquinoline derivatives **35** in good yields with high stereoselectivities (92–99% ee).



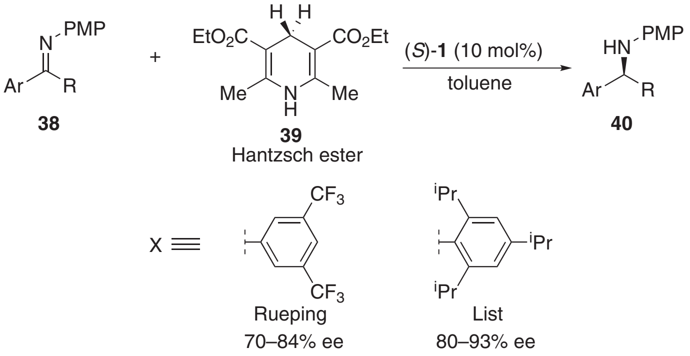
Scheme 11.9 Enantioselective Povarov reaction with vinylindole derivatives.

However, the optimum conditions for the reaction of 2-vinylindole could not be applied to that of 3-vinylindole (**36**) because of its high sensitivity to the acidic conditions. Several examinations revealed that the use of a coordinating solvent, such as tetrahydrofuran, and the slow addition of **36** over 12 h were crucial for this reaction; the desired cycloadducts **37** were then obtained in good yields with high stereoselectivities (73–97% ee).

11.2.4
Transfer Hydrogenation

The enantioselective reduction of the C=N double bond, such as those found in ketimines, is the most straightforward approach to synthesizing chiral amines. Most catalytic enantioselective hydrogenations of ketimines have been conducted using common hydrogen sources, such as high-pressure molecular hydrogen, alkylsilanes, and ammonium formate, in the presence of chiral transition metal complexes. List and coworkers and MacMillan and coworkers independently reported the organocatalytic transfer hydrogenations of α,β-unsaturated aldehydes using Hantzsch esters **39**, which are dihydropyridine derivatives, as the biomimetic hydrogen source (NADH mimic reagent) [19]. These excellent reports have propelled Hantzsch esters into the limelight as an efficient hydrogen source for enantioselective transfer hydrogenation.

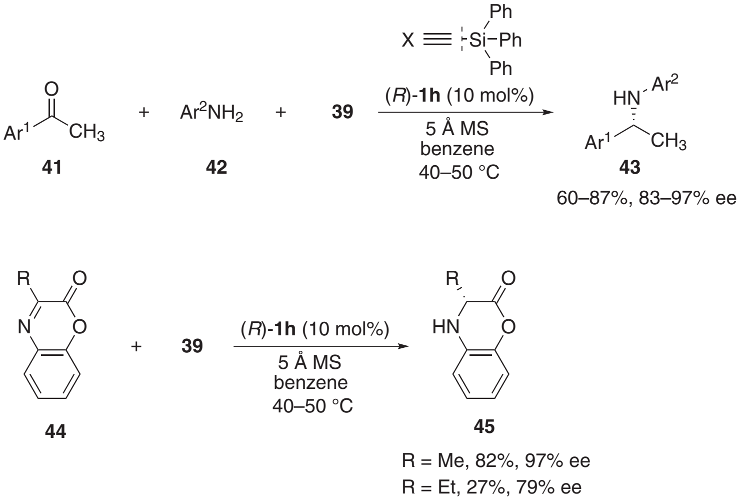
The first report of the combination of chiral phosphoric acid and Hantzsch ester **39** as the hydrogen source dealt with the asymmetric reduction of an imine derivative. Rueping's group and List's group independently found that the combination of **1** and **39** was very effective in the enantioselective transfer hydrogenation of ketimines (Scheme 11.10) [20, 21].



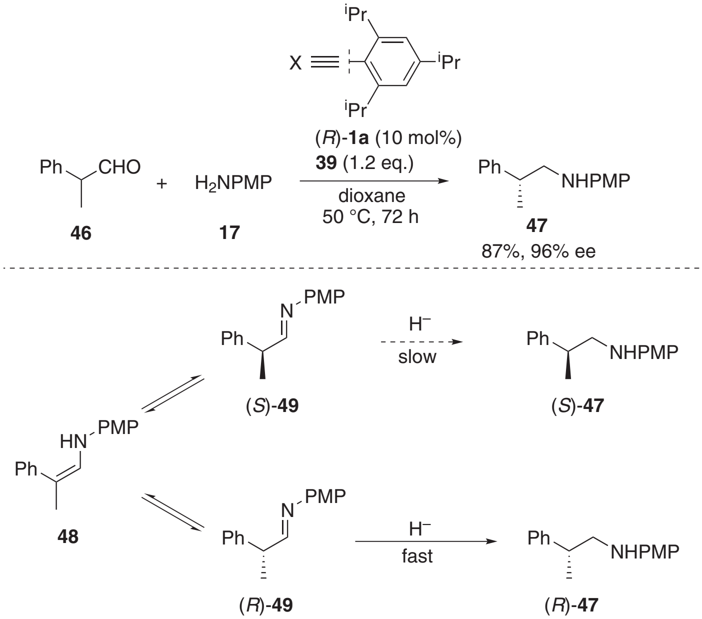
Scheme 11.10 Enantioselective transfer hydrogenation of ketimine.

At almost the same time, MacMillan and coworkers found that the reductive amination starting from aldehyde, amine, and Hantzsch ester **39** also proceeded smoothly by means of **1** in the presence of 5 Å MS to afford benzylic amines **43** with 83–97% ee (Scheme 11.11) [22]. They proved that dialkyl ketones as well as alkyl aryl ketones were suitable substrates; even methyl ethyl ketone was reductively aminated with 83% ee. They also reported the asymmetric reduction of pyruvic-acid-derived cyclic imino ester **44**. In this reaction, the structure of **44** exhibited a remarkable correlation to MM3 calculations in terms of both hydrogen bond orientation and specific architectural elements that dictate iminium enantiofacial discrimination.

List and coworkers developed an excellent application of this method to a dynamic kinetic resolution approach (Scheme 11.12) [23]. In the presence of phosphoric acid catalyst **1a** and **39**, the reductive amination of *racemic* α,α-disubstituted aldehydes **46** and *para*-anisidine (**17**) proceeded through a tautomerization between enamine **48** and imine **49**. The essential point of this protocol is that the hydrogenation of (*R*)-**49** proceeded more rapidly than that of (*S*)-**49** to give β-branched amine **47** in 87% yield with 96% ee.

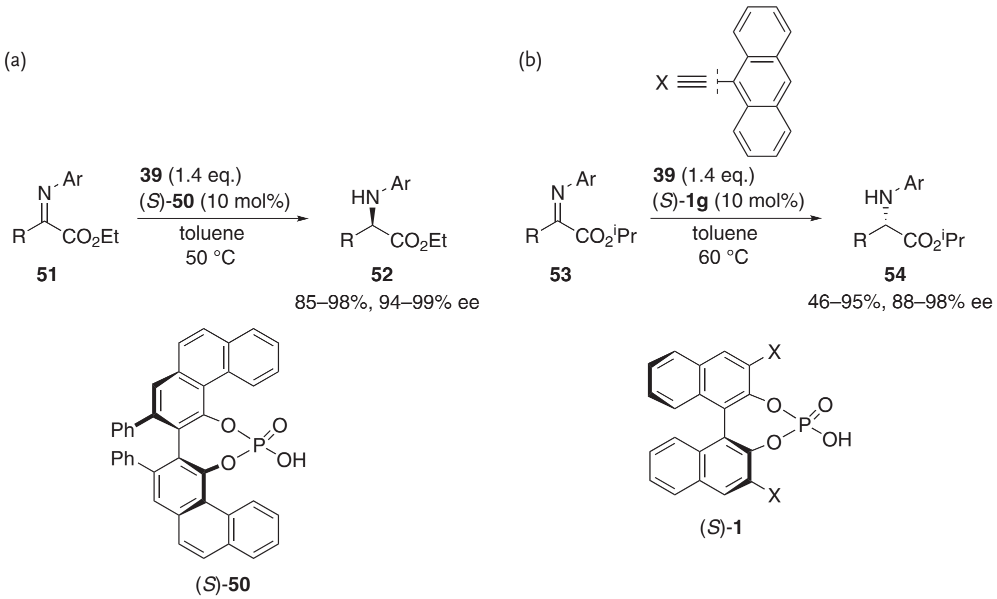


Scheme 11.11 Enantioselective reductive amination with Hantzsch ester **39**.



Scheme 11.12 Dynamic kinetic resolution approach to achiral phenethyl amine derivatives.

Antilla and coworkers also developed asymmetric transfer hydrogenation reaction by means of **50**, derived from VAPOL (Scheme 11.13) [24]. They realized the highly enantioselective transfer hydrogenation of acyclic α-imino ester **51** by the combination of **39** and **50** to furnish synthetically useful α-amino acid derivatives **52** in excellent enantioselectivities (94–99% ee). They also achieved reductive amination of alkyl-substituted ketimines (R = alkyl) in the presence of dehydrating agent (4 Å MS).

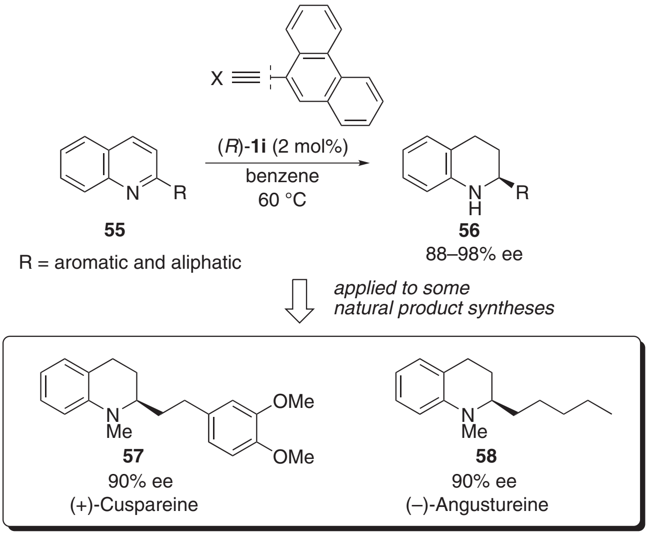


Scheme 11.13 Enantioselective synthesis of α-amino ester derivatives by **50**.

At almost the same time, You and coworkers developed the same type of asymmetric reaction by employing the binaphthyl phosphoric acid **1g**. In their case, the isopropyl ester group was the best substituent as for the enantioselectivity [25].

This type of asymmetric reduction became the topic of much interest and many excellent methods for the construction of chiral amine substructures were developed. Various pharmacologically important substructures, such as α-amino esters and tetrahydroquinolines, could be obtained with excellent enantioselectivities.

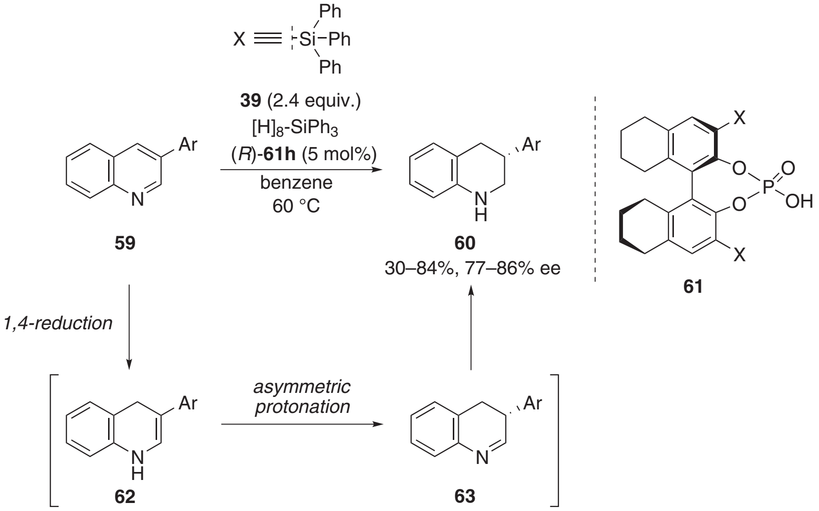
For example, Rueping and coworkers reported a highly enantioselective transfer hydrogenation of quinolines by means of **1** (Scheme 11.14) [26]. This method offered a wide variety of chiral quinolines with good to excellent enantioselectivities (88–98% ee) and low catalyst loading (2 mol%). Its elegant application to various isoquinoline alkaloids was also demonstrated.



Scheme 11.14 Asymmetric transfer hydrogenation of quinoline derivatives.

Rueping and Antonchick also showed that this type of asymmetric reduction could be applied to pyridine derivatives and the resulting piperidines were obtained with excellent selectivities (84–92% ee) [27].

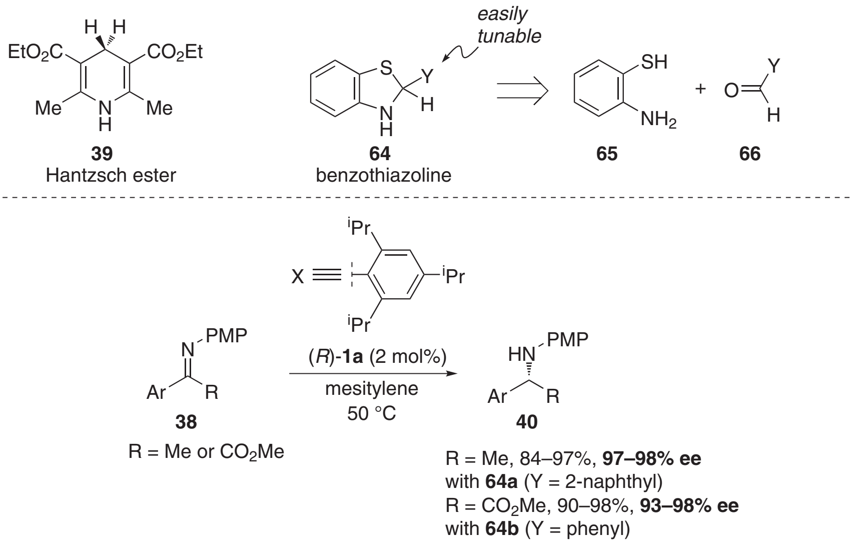
Rueping and coworkers further extended the method to the hydrogenation of 3-substituted quinolines **59** (Scheme 11.15) [28]. The mechanism of this



Scheme 11.15 Enantioselective synthesis of 3-substituted tetrahydroquinolines via asymmetric protonation.

transformation is totally different from that of the asymmetric hydrogenation of 2- or 4-substituted quinolines, in which the 1,2- or 1,4-hydride addition step is crucial in determining the stereochemical outcome. Quite interestingly, the enantioselective protonation of intermediary enamines **62** occurred effectively, leading to 3-substituted tetrahydroquinolines **60** with good enantioselectivities (77–86% ee).

As mentioned above, the asymmetric transfer hydrogenation of Hantzsch ester **39** could be applied to a wide variety of substrates, albeit with some limitations. One of the limitations of **39** is its tunability, which is a fatal drawback to broadening the generality of the asymmetric transfer hydrogenation reaction by **1** and **39**. In 2009, Zhu and Akiyama developed a highly tunable hydride source, benzothiazoline **64**, and showed that it could be used in the asymmetric transfer hydrogenation of ketimines by combination with chiral phosphoric acid catalyst **1** (Scheme 11.16) [29, 30].



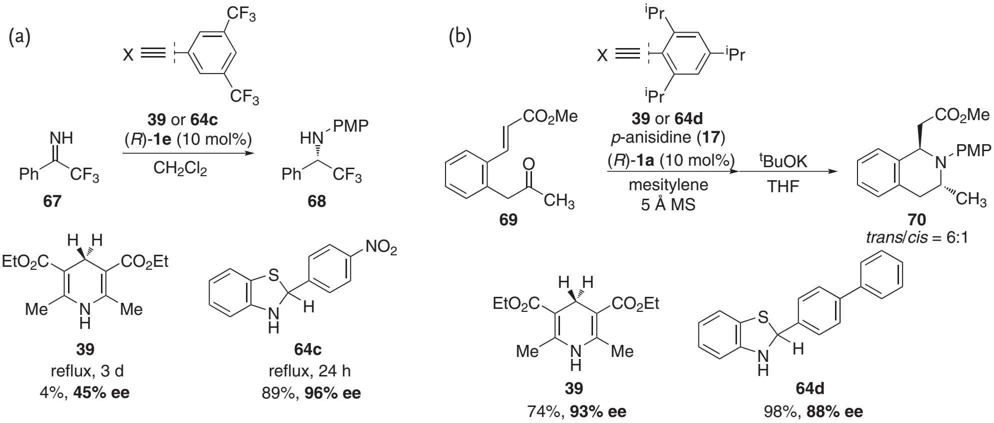
Scheme 11.16 Asymmetric transfer hydrogenation by benzothiazoline **64**.

Benzothiazoline **64** has two advantages:

1) Ease of preparation from commercially available materials, that is, 2-thioaminobenzene (**65**) and various aldehydes **66**;
2) ease of tuning the hydrogen transfer ability by changing the substituent (Y).

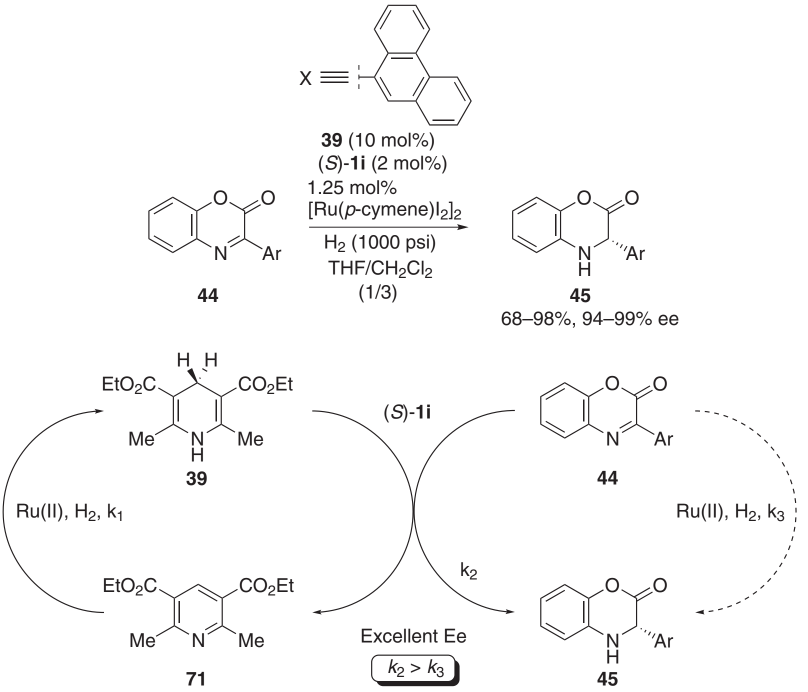
It is worth noting that the present method provides corresponding products **40** with higher enantioselectivities than those obtained in the previous report by List and coworkers (Scheme 11.10).

The high performance of **64** compared to Hantzsch ester **39** was demonstrated by Akiyama and coworkers in the asymmetric transfer hydrogenation of trifluoromethylacetophenone derivatives (Scheme 11.17a) [31]. Benzothiazoline **64c** afforded **68** in 89% yield with 96% ee. In contrast, a significant reduction of reactivity and enantioselectivity was observed when **39** was used (4% yield, 45% ee). Enders and coworkers also reported the superiority of benzothiazoline over Hantzsch ester in a symmetric synthesis of tetrahydroisoquinolines via the reductive amination/aza-Michael addition sequence (Scheme 11.17b) [32]. Benzothiazoline **64d** had a beneficial effect on both chemical yield and selectivity (98% yield, 88% ee versus 74% yield, 93% ee with **39**). Although the reason for the difference in reactivity is still unclear until, these results indicate the high potential of benzothiazolines as a hydride source.



Scheme 11.17 Some examples of the beneficial effect of benzothiazoline **64** compared with Hantzsch ester **39**.

One of the drawbacks of these types of hydride sources, such as Hantzsch ester **39** and benzothiazoline **64**, is the need to use a stoichiometric amount of reagent and the generation of the corresponding oxidized adduct (such as pyridine and benzothiazole derivatives). In 2011, Zhou and coworkers developed an efficient reaction system involving the catalytic transfer hydrogenation of benzoxazinone **44** by regenerating Hantzsch ester **39** *in situ* (Scheme 11.18) [33]. Interestingly, the reduction of benzoxazinone by Hantzsch ester and (*S*)-**1i** occurred overwhelmingly faster than that by Ru(II), and the H_2 system provided **45** with excellent enantioselectivity ($k_2 > k_3$).

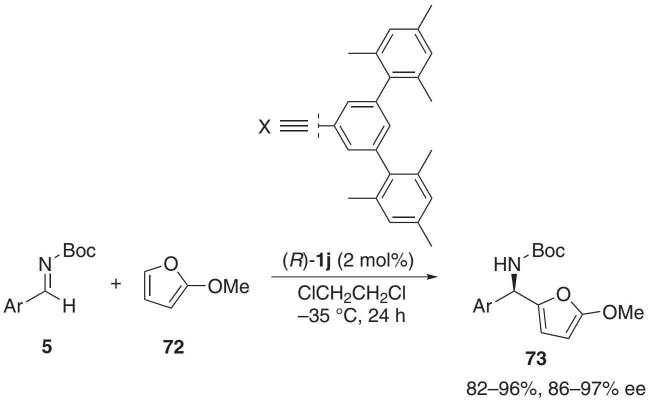


Scheme 11.18 Asymmetric transfer hydrogenation with regenerable Hantzsch ester **39**.

11.3
Friedel–Crafts Reaction

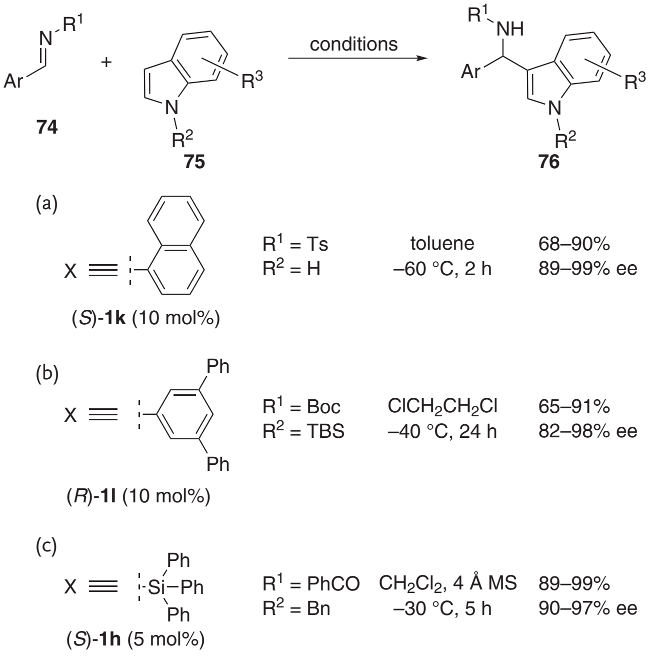
Enantioselective Friedel–Crafts reactions using metal-based chiral catalysts or chiral organocatalysts have been investigated extensively because the reactions directly provide alkylated arenes, a pharmacologically important substructure, in optically active forms. The chiral phosphoric acid catalyzed Friedel–Crafts reaction was first accomplished via the activation of imines but, currently, the scope of the electrophilic components has been broadened to include the Michael addition to nitroalkenes, α,β-unsaturated carbonyl compounds, and so on.

The first report of the enantioselective Friedel–Crafts reaction catalyzed by phosphoric acid **1** was presented by Terada and coworkers (Scheme 11.19) [34]. They reported the 1,2-aza-Friedel–Crafts reaction of 2-methoxyfuran (**72**) with *N*-Boc aldimines **5** by means of a catalytic amount of chiral phosphoric acid. In this reaction, sterically hindered 3,5-dimesitylphenyl-substituted catalyst **1j** was the most effective and the corresponding Friedel–Crafts adducts **73** were obtained with excellent enantioselectivities (86–97% ee). Notably, the reaction could be performed in the presence of as low as 0.5 mol% of **1j** without any loss of selectivity (Ar = Ph, 95% yield, 97% ee).



Scheme 11.19 Asymmetric Friedel–Crafts reaction of imines with 2-methoxyfuran.

Subsequently, the chiral phosphoric acid catalyzed Friedel–Crafts alkylation attracted much attention and became the subject of comprehensive investigations. In particular, the reaction with indole was investigated extensively because it provided pharmacologically important 3-substituted indole derivatives in enantiomerically enriched forms. The groups of You [35], Terada [36], and Antilla [37] almost simultaneously developed a highly enantioselective Friedel–Crafts reaction of indoles **75** with aromatic imines **74** (Scheme 11.20). Interestingly, their reactions



Scheme 11.20 Asymmetric Friedel–Crafts reaction of imines with indoles.

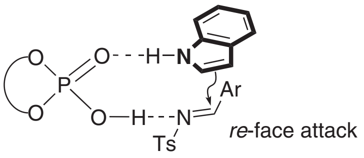


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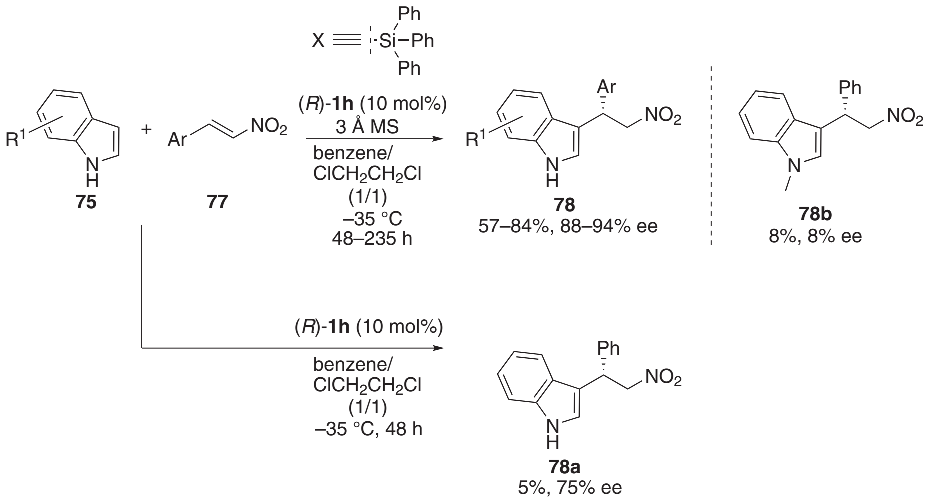
Figure 11.4 Calculated transition state model of an asymmetric Friedel–Crafts reaction.

have unique features: (i) substituents at the 3,3′-positions of the catalysts, (ii) the protective group of imines, and (iii) the presence or absence of a protective group at the nitrogen atom of indoles.

Simón and Goodman reported DFT calculations of the transition state model of *N*-tosyl imine and unprotected indole (Figure 11.4) [38]. In the transition state, the hydrogen bond network among the phosphoric acid, the imine, and the indole created an appropriate chiral environment for the highly stereoselective induction. Although the transition structure of the reaction with *N*-protected indoles is unclear (reported by Terada *et al.* [36] and Antilla *et al.* [37]), it is worth noting that high enantioselectivities were observed in the two reports.

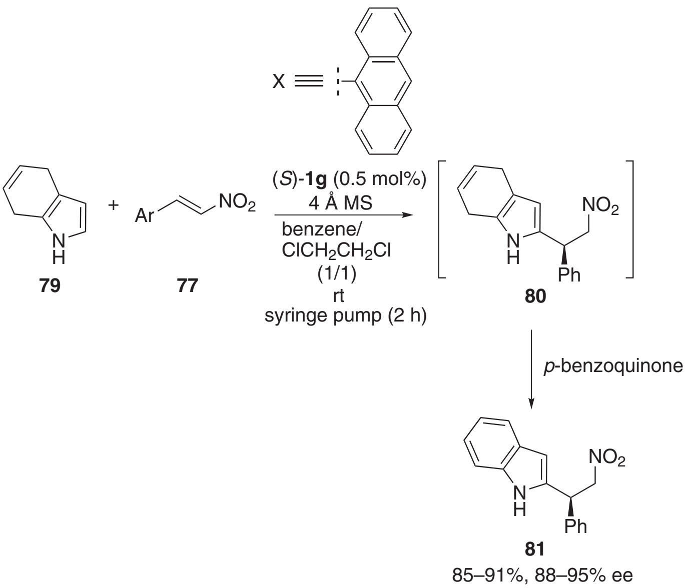
The enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes is one of the most important carbon–carbon bond-forming reactions for the preparation of biologically active compounds, such as indole alkaloids [39]. Although several chiral catalysts have been investigated for the reaction, the enantioselectivities are not always satisfactory. Akiyama and coworkers developed a highly enantioselective Friedel–Crafts reaction of nitroalkenes **77** with indoles **75** using chiral phosphoric acid **1h** (Scheme 11.21) [40]. They found that the addition of molecular



Scheme 11.21 Asymmetric Friedel–Crafts reaction of indoles with nitroalkenes.

sieves (3 Å MS) had a beneficial effect on both chemical yield and enantioselectivity, giving rise to Friedel–Crafts products **78** in good yields with high enantioselectivities. The method is applicable not only to aromatic nitroalkenes but also to aliphatic ones. They also pointed out the importance of retaining the N–H group in the indole derivatives as the reaction of *N*-methylindole provided racemic Friedel–Crafts product **78b** in low yield; hence, the *N*–H moiety of indoles is essential for accelerating the reaction as well as controlling the stereoselectivity.

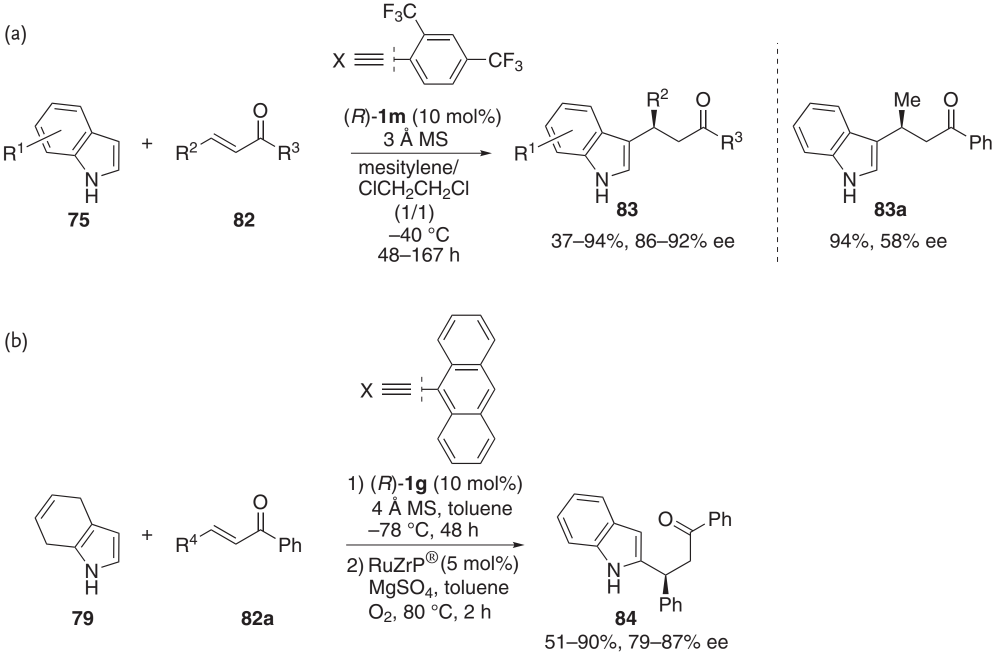
You and coworkers employed 4,7-dihydroindoles **79** instead of indoles **75** in the Friedel–Crafts reaction with nitroalkenes **77** (Scheme 11.22) [41]. Catalyst **1g** with a 9-anthryl group displayed excellent performance. The notable point in this reaction is the use of the syringe pump technique to achieve high enantioselectivities and suppress the background reaction. Subsequent oxidation of Friedel–Crafts adducts **80** by *p*-benzoquinone afforded 2-substituted indole derivatives **81** in excellent yields without racemization. This approach and the simple asymmetric Friedel–Crafts reaction of indoles are complementary methods for obtaining the different substitution patterns of chiral indole derivatives.



Scheme 11.22 Asymmetric Friedel–Crafts reaction of dihydroindole with nitroalkenes.

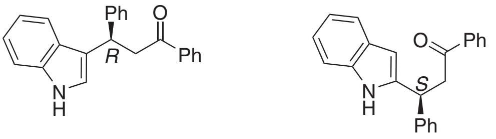
As mentioned above, a range of enantioselective transformations have been established using chiral phosphoric acids via the activation of imines and related nitrogen-substituted substrates. In contrast, the activation of carbonyl compounds, including α,β-unsaturated carbonyl compounds, by chiral phosphoric acids has been limited. In 2008, Zhou, He, and coworkers achieved the asymmetric Friedel–Crafts alkylation reaction of indole derivatives with 1,3-diaryl α,β-unsaturated ketones by means of **1d** with a *p*-chlorophenyl group at the 3,3′-positions, although the chemical yields and enantiomeric excesses did not reach satisfactory levels (up to 56% ee) [42].

In 2010, Akiyama and coworkers reported the highly enantioselective Friedel–Crafts reaction of indoles with α,β-unsaturated ketones (Scheme 11.23) [43]. They found that minute tuning of the reaction conditions is crucial to achieve the excellent selectivity. Treatment of **75** and **82** with **1m** having 2,4-$(CF_3)_2C_6H_4$ at the 3,3′-positions in a mixed solvent system (mesitylene/1,2-dichloromethane = 1 : 1) at –40 °C provided desired Friedel–Crafts adducts **83** in good chemical yields with excellent enantioselectivities (86–92% ee). The only exception was the reaction with 1-phenylbut-2-en-1-one (94% yield, 58% ee). They also studied the enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles **79** with 1,3-diaryl α,β-unsaturated ketones. In this case, 9-anthryl-substituted catalyst **1g** turned out to be the catalyst of choice, furnishing desired 2-substituted indoles **84** in good yields with good enantioselectivities after oxidation by RuZrP® (79–87% ee).



Scheme 11.23 Asymmetric Friedel–Crafts reaction of indole derivatives with 1,3-diaryl α,β-unsaturated ketones.

One interesting feature of these reactions is that the absolute configurations of the corresponding adducts were switched by employing the same (*R*)-phosphoric acid catalysts in both Friedel–Crafts reactions. In the case of dihydroindole, the enriched enantiomer was the (*S*)-enantiomer, whereas the (*R*)-isomer was the major product in the indole Friedel–Crafts reaction (Figure 11.5).



83 **84**

Figure 11.5 Absolute stereochemistry of Friedel–Crafts adducts **83** and **84**.

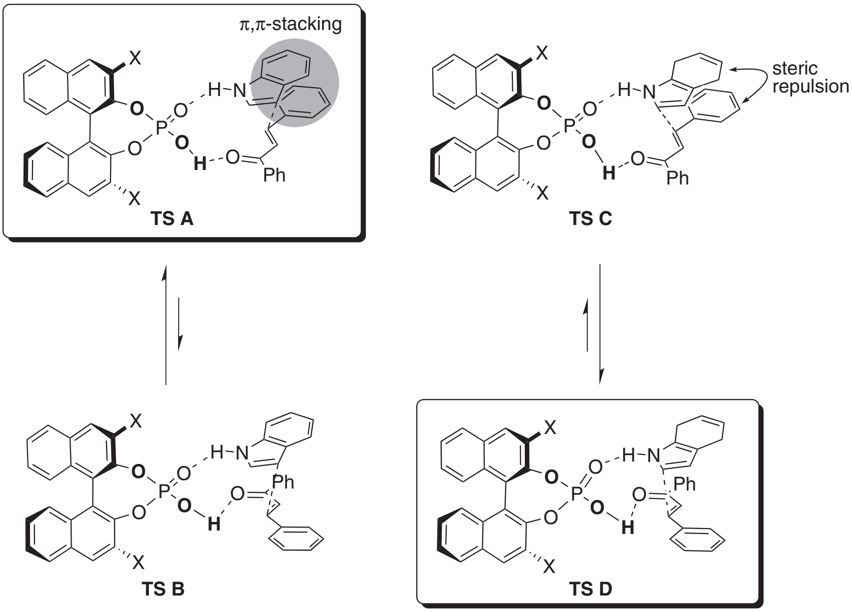
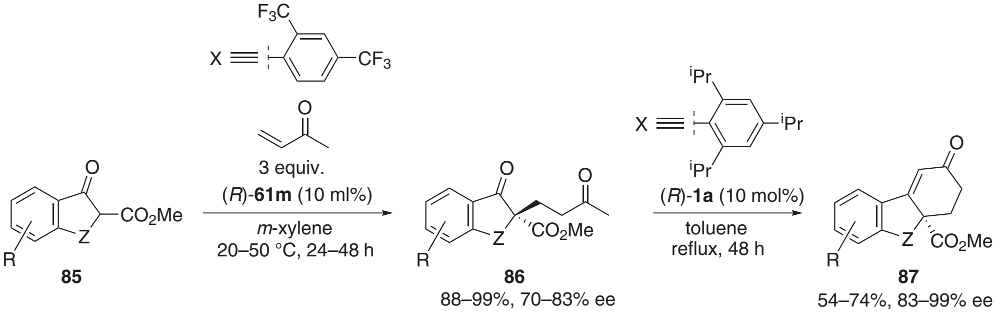


Figure 11.6 Proposed transition state model of the Friedel–Crafts reaction of indole.

Akiyama and coworkers explained this reversal of facial selectivity as follows. The key element is the difference in the direction of the α,β-unsaturated ketone. In the case of indole **75**, TS A was preferred over TS B because of the π,π-stacking between the indole benzene ring and the benzene ring at the 3-position of the chalcone moiety. In contrast, in the case of 4,7-dihydroindole **79**, the collapse of aromaticity led to severe steric repulsion (Figure 11.6), furnishing TS D as the predominant transition state. The low selectivity in the reaction of indole with 1-phenylbut-2-en-1-one clearly showed the importance of the π,π-stacking in the transition state.

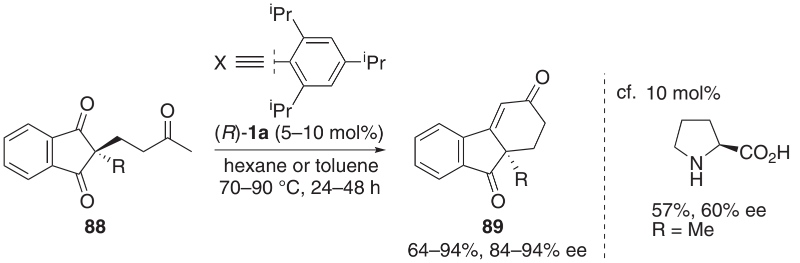
11.4
Intramolecular Aldol Reaction

The Robinson annulation reaction is one of the most fundamental methods for the construction of cyclohexenone structural motifs, which are frequently encountered in a number of natural product syntheses. Akiyama and coworkers developed a novel strategy for the enantioselective Robinson annulation reaction, which consisted two enantioselective processes: (i) a chiral Brønsted acid catalyzed enantioselective Michael addition reaction of β-keto esters **85** with methyl vinyl ketone and (ii) a chiral Brønsted acid catalyzed kinetic resolution in the intramolecular aldol reaction, followed by dehydration (Scheme 11.24) [44]. The enantiomer obtained selectively by the Michael addition reaction reacted preferentially to give corresponding Robinson-type annulation products **87** with excellent enantioselectivities (83–99% ee).



Scheme 11.24 Enantioselective Robinson-type reaction.

Akiyama and coworkers extended this methodology to the desymmetrization of *Cs*-symmetric-1,3-diones **88** (Scheme 11.25) [45]. In this process, an intramolecular aldol reaction and dehydration occurred successively to afford cyclohexenone derivatives **89** with excellent enantioselectivities (87–94% ee). Notably, the selectivity of chiral phosphoric acid **1a** is much higher than that of (*S*)-proline (60% ee), which is commonly used as a highly reliable chiral catalyst for the desymmetrization of *Cs*-symmetric-1,3-diones.



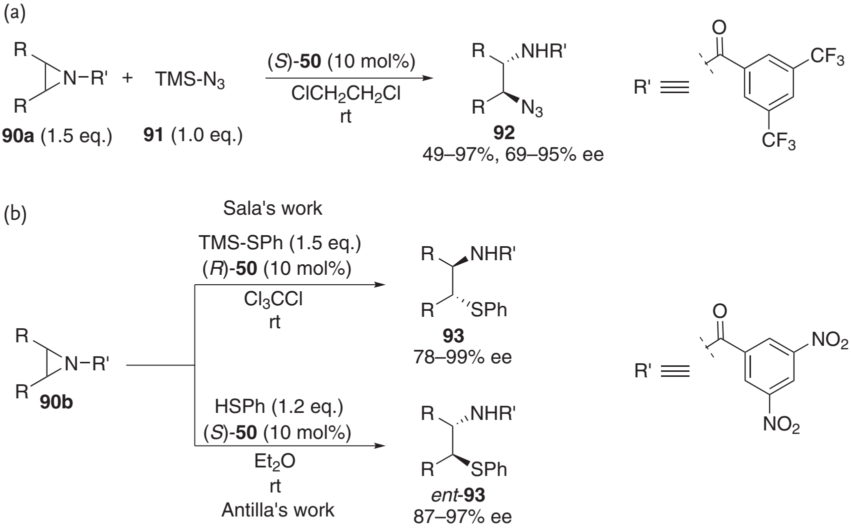
Scheme 11.25 Chiral phosphoric acid catalyzed desymmetrization reaction of a 1,3-dione.

The same authors proposed the origin of this high selectivity by a computational method, namely, ONIOM (B3LYP/6-31G*:HF/3-21G) calculations. In the TS, chiral phosphoric acid simultaneously activated both carbonyl and enol moieties with Brønsted acidic and Lewis basic sites, respectively. Owing to the steric repulsion between the aryl moiety of the substrate and the triisopropylphenyl group at 3,3′-positions, the attack of the TS from the *Re*-face was 1.3 kcal mol^{-1} more unstable than attack from the *Si*-face, giving rise to the preferential formation of the (*S*)-enantiomer.

11.5
Ring Opening of *meso*-Aziridines

Chiral vicinal diamines are found in anticancer agents and anti-influenza drugs, as well as many other biologically active compounds. A range of methods for the synthesis of these diamines have been developed. One of the most direct methods for their synthesis is the ring-opening of aziridines with nitrogen nucleophiles. While many of these existing strategies have been successful, the development of catalytic, enantioselective methods for the opening of *meso*-aziridines has been much less studied.

In 2007, Antilla and coworkers developed the first example of a Brønsted acid-catalyzed enantioselective ring-opening of *meso*-aziridines [46]. Various chiral amino azides **92** were obtained in good to excellent enantioselectivities by means of VAPOL-derived phosphoric acid **50** (69–95% ee) (Scheme 11.26). The protecting group on the nitrogen played a critical role in realizing high enantioselectivity, and bis(3,5-trifluoromethyl)benzoyl was the best substituent.



Scheme 11.26 Chiral phosphoric acid catalyzed asymmetric ring opening of *meso*-aziridines.

At almost the same time, the groups of Sala [47] and Antilla [48] independently extended this methodology to the construction of β-aminosulfur compounds. VAPOL-derived phosphoric acid **50** was effective in both cases; the good to excellent selectivities could be achieved by employing the 3,5-dinitrobenzolyl group on nitrogen. In Sala's report, TMS-protected thiophenol was employed for enhancement of the reactivity, whereas Antilla and coworkers achieved with free thiol moiety with the same catalyst system.

11.6
Future Prospects

Phosphoric acid was found to work well as a versatile organocatalyst for a range of asymmetric transformations. Initially, the catalyst was utilized for imines in most cases because it could be activated by a Brønsted acid catalyst. Today, various types of bond-forming reactions, including the reactions of various types of electrophilic moieties with nucleophiles, have been successfully established by chiral phosphoric acids. However, this type of catalyst has limitations, including the weak acidity and the requirement of relatively high catalyst loading (around 5–10 mol%). Recently, various stronger Brønsted acid catalysts were developed by Nakashima and Yamamoto [49], Ishihara and coworkers [50], and List and coworkers [51, 52], which enabled the realization of a range of new transformations. The elaboration of novel chiral Brønsted acids derived not only from other types of chiral backbones but also from stronger acid functionalities could lead to the discovery of even more selective and efficient methods for a wide variety of enantioselective transformations.

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12
Brønsted Acids: Chiral (Thio)urea Derivatives

Gergely Jakab and Peter R. Schreiner

12.1
Introduction

12.1.1
Explicit Double Hydrogen-Bonding Interactions

(Thio)urea organocatalysts display great structural diversity and show pronounced catalytic activity in a broad spectrum of reactions [1]. In fact, for almost every synthetic problem addressed in the second part of this volume a suitable (thio)urea catalyst can be found. Therefore, it is imperative to present a general overview of this important catalyst class, and to attempt to rationalize its modes of action. Hine *et al.* laid the foundation of this field in 1984 by recognizing the importance of explicit double hydrogen-bonding interactions; X-ray crystallographic studies revealed that Lewis basic compounds, such as hexamethylphosphoramide, accept two H-bonds in a clamp-like manner from 1,8-biphenylenediol (Figure 12.1, I) [2]. This finding initiated a mechanistic study of the aminolysis of epoxides involving 1,8-biphenylenediol and phenol derivatives as catalysts. The superior efficiency of explicit double H-bonding catalysts over monodentate H-bond donors was demonstrated: two equivalents of a monodentate catalyst 600 times more acidic than 1,8-biphenylenediol were needed to match its reaction rate enhancement [3]. Inspired by these results, Kelly and coworkers synthesized an electron-deficient 1,8-biphenylenediol derivative to promote the Diels–Alder reaction of α,β-unsaturated aldehydes and ketones with dienes [4]. In an apparently unrelated investigation, Jorgensen and coworkers studied Diels–Alder reactions [5] and Claisen rearrangements [6] by computational methods. They elucidated the beneficial effect of water on reaction rates compared to apolar solvents, and devised a solvation model (Figure 12.1, II). According to this model two water molecules simultaneously establish H-bonds to the carbonyl oxygen of the substrate for optimal transition state stabilization. The concept of explicit double H-bonding activation was no longer restricted to one type of reaction or catalyst, but became a generally applicable principle.

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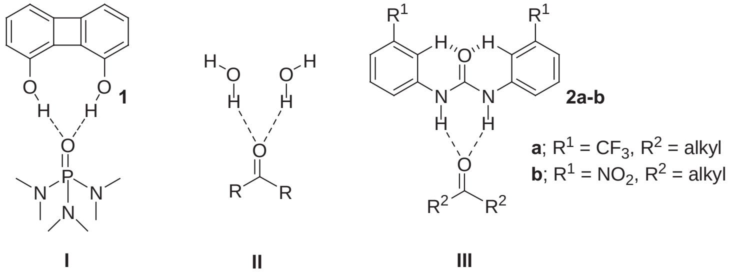


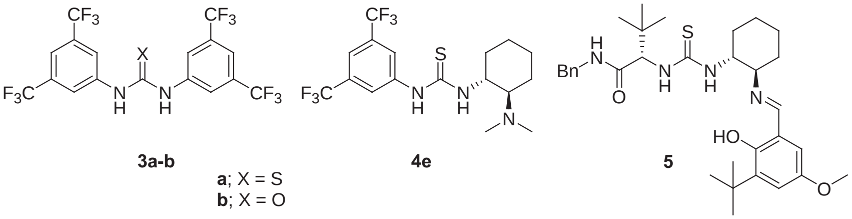
Figure 12.1 Early examples of explicit double H-bonding interactions.

12.1.2
The Beginnings of (Thio)urea Catalysis

Before (thio)urea derivatives were used as catalysts, their ability to establish strong hydrogen bonds with various ions [1f, 7] had already been recognized. In 1990 Etter and coworkers co-crystallized *N,N′*-diphenylureas with Lewis basic compounds such as triphenylphosphine oxide, nitroaromatics, ethers, ketones, and sulfoxides (Figure 12.1, III) [8]. It was found that electron-deficient urea derivatives formed more stable complexes, due to an enhanced H-bond donor ability [8]. Later Wilcox and coworkers investigated the recognition ability of various (thio)urea derivatives toward sulfonates, phosphonates, and carboxylates [9]. In contrast to the aforementioned co-crystallization study, nitro substituents in the *para* position proved more effective than those at the *meta* position. These complexation studies showed that the (thio)urea group has a certain affinity to Lewis basic functional groups, and the interaction between them resembles the clamp-like double H-bonding observed with 1,8-biphenylenediol derivatives. The first attempt to exploit this similarity was made by Curran and Kuo, who introduced an *N,N′*-diphenylurea-catalyzed alkylation of α-sulfinyl radicals [10]. The method was later extended to Claisen rearrangements [11]. Although the acceleration effect was moderate (22-fold with 100% catalyst loading), an important observation was made to underline the relevance of double H-bond donating ability. The *N,N′*-dialkylurea catalyst and a corresponding benzanilide were shown to have a very limited effect on reaction rates, even in stoichiometric amounts. Despite its potential, no systematic further development had been made to this field until 1998, when the Schreiner group began its investigations [12]. Thiourea derivatives were chosen over ureas for practical reasons, such as better solubility in many organic solvents, higher acidity (urea $\mathrm{p}K_\mathrm{a} = 26.9$, thiourea $\mathrm{p}K_\mathrm{a} = 21.1$, in DMSO) [13], decreased aptitude for self-association, and synthetic ease. As a modification to Curran's catalyst *N,N′*-bis[3-(trifluoromethyl)phenyl]thiourea was synthesized and found to promote the Diels–Alder reaction between methyl vinyl ketone and cyclopentadiene (1% catalyst loading) [14, 15]. Moderate rate enhancement was observed even in water, showing that the catalyst competed successfully with the solvent molecules for the substrates. In 2003 Schreiner and Wittkopp conducted a detailed investigation to reveal structure–reactivity relations in Diels–Alder reactions catalyzed by a series of thiourea derivatives [15]. As anticipated, electron-deficient catalysts promoted the reaction more than electron-rich derivatives. Electron-withdrawing groups, such as trifluoromethyl (CF_3) in aromatic *para* or *meta* positions, had the strongest beneficial effect on the reaction rates, while substituents in the *ortho* position had a smaller influence. There was no evidence for product inhibition owing to the weak enthalpic binding between the catalyst and carbonyl groups (~7 kcal mol^{-1} at room temperature) [16]. With a weak binding enthalpy, the entropy term of complex formation is more difficult to overcome; thus catalysts with somewhat rigid structures are more favorable. Electron-withdrawing groups in the phenyl ring's *para* or *meta* position increase the polarization of *ortho*-hydrogens, leading to intramolecular H-bonds as depicted in Figure 12.1, and thereby effectively hinder rotation around the C–N bond [15]; Etter's X-ray crystallographic study also supports this concept [8]. In the first review of the topic one of us summarized these findings and proposed some guidelines for future catalysts [1b]:

1) as always in catalysis, if the catalyst can interact with the starting material, the transition state (TS), and the products, it is necessary that the relative stabilization of the TS is the largest; this can be probed by computational methods;
2) the bi- or multidentate mode of catalyst–substrate binding increases catalytic efficiency and restricts degrees of freedom;
3) the catalyst structure should be somewhat rigid;
4) to avoid self-association the catalyst should not incorporate strong hydrogen bond acceptors such as ester or nitro groups; the non-coordinating acidifying CF_3 group as in the 3,5-(trifluoromethyl)phenyl moiety is an excellent choice in this respect [17];
5) weak enthalpic interactions reduce product inhibition, allowing substoichiometric amounts of the catalyst;
6) the catalyst should ideally be water compatible or even catalytically active in water[1b, 1g].

During the last decade numerous applications have appeared in the literature concerning Schreiner's symmetrical thiourea catalyst (Figure 12.2). Examples



3a-b

a; X = S
b; X = O

4e

5

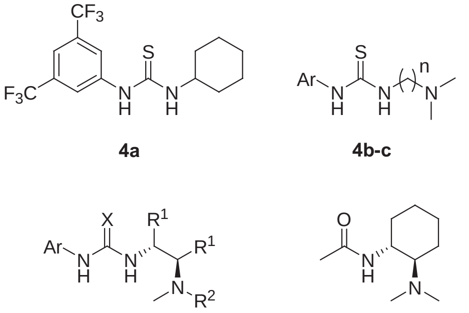
Figure 12.2 Schreiner's thiourea (**3a**), Takemoto's bifunctional catalyst (**4e**), and Jacobsen's "ligand" (**5**).

include the nucleophilic addition of trimethylsilyl cyanide and ketene silyl acetals to nitrones or aldehydes [18], Friedel–Crafts alkylation of indoles [19], acylcyanation of imines [20], aldehydes, and amines [21], transfer hydrogenation of aldimines [22], reduction of conjugated nitroalkenes [23], and the Corey–Chaykovsky reaction [24], to simply highlight some applications from a long list [18–25]. The Jacobsen group followed a different course of research, which originally aimed at tridentate ligands to promote organometallic asymmetric Strecker reactions [26]. In some cases catalytic activity was observed in the absence of metal, and high-throughput screening led to an optimized structure yielding the first enantioselective thiourea organocatalyst in 1998 (92% yield, 91% ee, Figure 12.2). These early and ground-breaking examples paved the way for new catalyst generations and led to a vast number of representatives. The ubiquity of the (thio)urea catalyst class is rationalized by two simple factors. First, (thio)urea derivatives can usually be prepared in a couple of straightforward steps, and do not pose great synthetic challenges. The most common chiral building blocks such as proline [27], cinchona alkaloids [28], and 1,2-diaminocyclohexane [29] readily undergo transformations leading to the corresponding catalysts. Second, the (thio)urea moiety is often involved in multifunctional catalysis, which requires synergistic activation and orientation of reactants leading to superior reaction control. The first chiral bifunctional thiourea catalyst was synthesized in 2003 by Takemoto and coworkers (Figure 12.2) [29]. Connon highlighted the most important stages of catalyst evolution in his 2009 review [30].

12.2
Important Chiral (Thio)urea Organocatalysts

12.2.1
Takemoto's Catalyst

Takemoto's catalyst consists of a double H-bond donor thiourea moiety ($pK_a = 13.65$ in DMSO) [13b], the privileged 3,5-bis(trifluoromethyl)phenyl group [16, 17], and a basic tertiary amine built on a *trans*-1,2-diaminocyclohexane framework, which provides the chiral environment for stereoselective catalysis. Since its discovery in 2003 Takemoto's bifunctional catalyst has been applied to a broad spectrum of reactions. It was proven to be effective in Michael [29, 31], aza-Michael [32], and aldol reactions [31p], [3+2] cycloadditions [33], oxyaminations [34], cyclocarbohydroxylations [35], nitrocyclopropanations [36], and Neber- [37], Strecker- [38], Mannich- [32, 39], aza-Henry- [40], aza-Morita–Baylis–Hillman-like- [41], and Friedel–Crafts reactions [42], 1,2-sulfone rearrangements [43], and the synthesis of 4*H*-pyran derivatives [44]. It was also applied in the synthesis of natural products such as: (*R*)-(−)-baclofen[31a], (−)-epibatidine [31t], 3,4-dihydrocoumarines [31d], (−)-lycoramine [31f], (−)-galanthamine [31f], and (+)-lunarine [31f]. As the first representative of the bifunctional (thio)urea organocatalyst family, it was extensively studied to reveal the details of its modes of action. Miyabe and



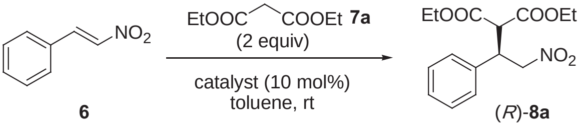
4a **4b-c** **4d-n** **4o**

b; Ar = 3-$CF_3C_6H_4$, n = 2
c; Ar = 3-$CF_3C_6H_4$, n = 3
d; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = Ph, Ph, R^2 = Me
e; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Me
f; X = S, Ar = 3-$MeOC_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
g; X = S, Ar = 3-CNC_6H_4, R^1 = $(CH_2)_4$, R^2 = Me
h; X = S, Ar = 3-$CF_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
i; X = S, Ar = Ph, R^1 = $(CH_2)_4$, R^2 = Me
j; X = S, Ar = 2-$CF_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
k; X = S, Ar = 4-$CF_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
l; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = ^{i}Pr
m; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Bn
n; X = O, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Me

Figure 12.3 Structure of catalysts [31a].

Takemoto summarized their findings in 2008 and provided general guidelines for bifunctional catalyst development [45]. First a number of structurally similar catalysts (Figure 12.3) were synthesized and tested in the Michael addition of diethyl malonate to nitrostyrene (Table 12.1) to unravel structure–reactivity–selectivity relations [31a]. Organic bases showed low activity in the reaction, even with **4a** present the conversion was moderate. No selectivity and low conversions were observed when the basic function was attached to the molecule with a flexible alkyl chain (**4b**, **4c**). This lack of activity can be interpreted on the basis of the principles outlined above: the relatively weak binding interactions demand a certain level of rigidity from the catalysts to reduce entropic loss upon substrate binding. Furthermore, these findings demonstrate that bifunctional catalysis means more than having different functional groups in a molecule – a well-defined spatial alignment is essential. Indeed, applying the more rigid 1,2-diaminocyclohexane framework resulted in high conversion and selectivity. After the most suitable chiral backbone was identified, the substituent effect was investigated. Replacing electron-withdrawing CF_3 groups with hydrogens or electron-donating MeO groups on the aromatic ring slightly lowered selectivity and activity due to weaker H-bonding ability. In contrast, urea derivative **4n**, which is significantly less acidic than thiourea catalysts **4a–m** [13], promoted the reaction with almost

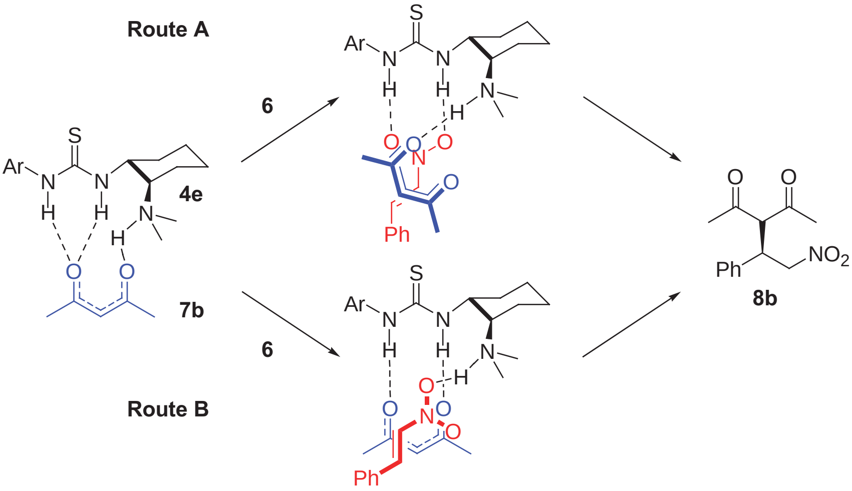
Table 12.1 Michael addition of diethyl malonate to nitrostyrene promoted by various catalysts [31a]$^{a)}$.



Entry	Additive	Time (h)	Yield (%)$^{b)}$	ee (%)$^{c),d)}$
1	TEA	24	17	–
2	DBU	3	13	–
3	TEA + **4a**	24	57	–
4	**4b**	48	38	–
5	**4c**	48	43	–
6	**4d**	48	52	64
7	**4e**	24	86	93
8	**4f**	48	69	74
9	**4g**	48	88	83
10	**4h**	48	78	84
11	**4i**	48	58	80
12	**4j**	24	72	72
13	**4k**	48	88	77
14	**4l**	48	76	87
15	**4m**	48	38	89
16	**4n**	24	87	91
17	**4o**	24	14	35

a) The reaction was conducted with **6** (1 equiv), **7a** (2 equiv), and toluene in the presence of various additives (10 mol%) at room temperature.
b) Yield of isolated product.
c) Enantiomeric excess was determined by HPLC analysis of **8a** using a chiral column.
d) Absolute configuration was determined by comparing the specific rotation of **8a** with that of literature data.

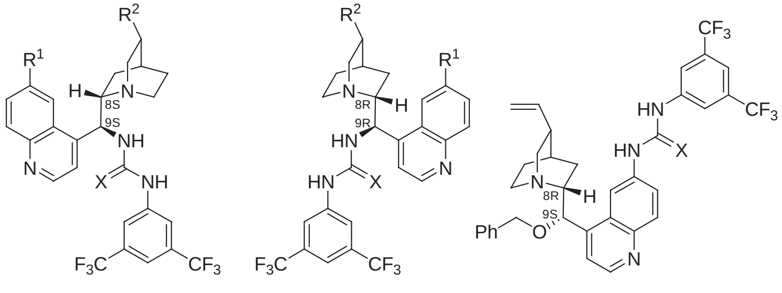
the same efficiency as **4e**. The steric hindrance around the basic function was increased in **4l** and **4m**, which resulted in a decreased activity but similar selectivity. The monodentate H-bond donor **4o** promoted the reaction with limited conversion and selectivity, underlining the necessity of the double H-bonding (thio)urea group. Mechanistic investigations showed that the reaction is first order in both reactants and the catalyst. Furthermore, **4e** was mixed with its enantiomer in different ratios, and the enantiomeric excess of the product was found to correlate linearly to that of the catalyst, suggesting a monomeric active form. Pápai and coworkers conducted a theoretical investigation of the Michael addition of acetylacetone to nitrostyrene, focusing on the transition states and the origin of selectivity at catalyst **4e** [46]. The first question concerned the conformation of the free catalyst prior to substrate binding. X-Ray crystallographic measurement showed that in the solid phase the catalyst adopted a conformation where the thiourea hydrogens and the tertiary amine group oriented in the same direction [31a]. This alignment is considered favorable for substrate binding and activation. Computations, however, yielded other similarly stable conformers in solution, suggesting that the catalyst exists in an equilibrium of different conformers and does not necessarily adopt the catalytically active conformation in its uncomplexed form. Both nitrostyrene and acetylacetone form similarly stable double H-bonding complexes with the neutral catalyst, but protonation of the tertiary amine group is more likely to occur if acetylacetone is supported by additional H-bonds. This leads to two plausible reaction pathways (Scheme 12.1) depending on which site binds nitrostyrene. Comparing the overall energetics of these two reaction routes the activation barrier for C–C bond formation in path B was found to be notably lower than that in A. According to this the reaction proceeds primarily through path B. The two depicted transition structures yield the product in the (*R*)-configuration. To understand the selectivity of the reaction, path A′ and B′ leading to the (*S*)-product configuration was also investigated. All four ternary complexes exhibited similar stability, but the activation barrier of C–C bond formation turned out to be 2.6 and 2.4 kcal mol^{-1} higher for path A′ and B′, respectively. This prediction is in line with the experimental observation that catalyst **4e** produces the (*R*)-enantiomer with high selectivity (89%) [31a]. The study implies that the mode of activation is not restricted to this catalyst but it is generally applicable to bifunctional organocatalysts bearing a (thio)urea and a tertiary amine functional group.



Scheme 12.1 Two reaction routes envisioned for the Michael addition of acetylacetone (**7b**) to nitrostyrene (**6**) [46]. Note that both pathways lead to the formation of the (*R*) configuration of the Michael adduct **8b** in the present arrangement of the substrates.

12.2.2
Cinchona Alkaloids in (Thio)urea Organocatalysis

Cinchona alkaloids make an excellent choice for chiral scaffolds. Even the naturally occurring representatives have organocatalytic potential [47] owing to their basic quinuclidine group and H-bond donor hydroxyl moiety. Although cinchona alkaloids have five stereogenic centers, only the configuration of C8 and C9 positions has catalytic relevance. Inverted structures around these positions typically favor the opposite stereochemical outcome of a reaction, and therefore are called pseudo-enantiomers; note that these catalysts are in fact diastereomers with differing catalytic performance in some cases. Pseudo-enantiomeric cinchona alkaloids are equally abundant in nature, unlike some of the other commonly used chiral pool molecules (e.g., amino acids). This accessibility made a large contribution to the success of this catalyst family. Inspired by the latest advancements in explicit double H-bonding catalysis [1b], four independent research groups developed cinchona-based (thio)urea derivatives (Figure 12.4) in 2005 [28, 48]. Chen and coworkers introduced a thiourea moiety to cinchona alkaloids by synthesizing catalyst **10c** and applied it in the Michael additions of phenylthiol to unsaturated imides with limited success [48c]. Soós and coworkers prepared catalysts **9a,b** and **10a,b** (**9a**, pK_a = 12.39 in DMSO [13b]) in a straightforward two-step procedure [28], similar to Chen's, and chose the Michael addition of nitromethane to chalcones as test reaction [28]. They found that nitromethane applied as solvent enabled low catalyst loadings (2–3%) and reasonable reaction times (27–45 h), while the selectivity of the reaction remained excellent (92% ee). Only marginal loss of enantiomeric excess (85% ee) was observed at reaction temperatures as



9a-e **10a-e** **11**

a; X = S, R^1 = OMe, R^2 = vinyl
b; X = S, R^1 = OMe, R^2 = ethyl
c; X = S, R^1 = H, R^2 = vinyl
d; X = S, R^1 = H, R^2 = ethyl
e; X = O, R^1 = OMe, R^2 = vinyl
f; X = O, R^1 = OMe, R^2 = ethyl

Figure 12.4 Cinchona derived (thio)urea catalysts.

high as 100 °C. Both electron-withdrawing and -donating substituents on chalcone were tolerated; pseudo-enantiomeric catalysts **10a** and **10b** gave the opposite stereomer products with similar selectivity. Note that C9 epimers of the active catalysts, which resemble the naturally occurring alkaloid configuration, were completely inactive under these conditions. Connon and coworkers examined the addition of dimethyl malonate to nitroolefins promoted by the same catalysts, and reported that **9b** and **10b** were the most effective (**9b**, 98% conversion, 90% ee) [48a]. The diminished H-bond donor ability resulted in somewhat lower selectivity with urea derivatives **9f** (88% ee) and **10f** (79% ee). The different orientation of functional groups proved to have a more serious impact; catalysts epi-**9f** and epi-**10f** were inferior in terms of activity (25–26% conv.) and selectivity (17–26% ee). At the same time Dixon and coworkers prepared several cinchonine-based catalysts, and applied them in the addition reaction of dimethyl malonate to nitroolefins [48b]. Compared to the monodentate cinchona derivatives, double H-bonding thiourea catalyst **10c** showed superior performance in this transformation (98% conv., 94% ee). These ground-breaking studies identified the most promising candidates for a new class of (thio)urea catalysts and were summarized by Connon [49]. Furthermore, the importance of the C8–C9 configuration of the cinchona scaffold was pointed out. Since their discovery many new applications have been presented, where either configuration proved to be the catalyst of choice. Note that in most of these reactions the performance of these catalysts is similar due to their closely related structures. The following examples are assigned to the catalyst that was the most efficient in the given transformations. Catalysts **9a** and **10a** appeared to be the best in aza- [50], oxy- [51], and sulfa- [52], Michael additions [53], Michael–Henry [54], Michael–Knoevenagel [55], Michael–aldol [56], Mukaiyama–aldol [57], Friedel–Crafts- [58], Diels–Alder- [59], vinylogous aldol- [60], aza-Henry- [61], and Mannich reactions [62], dynamic kinetic resolutions [63], cyanosilylation- [64], cyclo-etherification [65], desymmetrization [66], oxazolone addition [67], [1,3] dipolar cycloaddition [68], cooperative catalysis with secondary amines [69], with fluoride anion in direct nucleophilic acylation of nitroalkenes [70], or with amino acids [71]. They were also involved in natural product syntheses: (*S*)-ibuprofen [52a], (*S*)-naproxen [52a], (20*S*)-7-ethyl-10-hydroxycamptotecin [64], and γ-butyrolactones [72]. Catalysts **9c** and **10c** showed the best results in the following: Michael addition [48b, 73], aldol cyclization [74], hydrophosphonylation [75], and Friedel–Crafts reaction [76]. Catalysts **9b** and **10b** were most efficient in: Michael additions [28, 48a, 77] and in Diels–Alder [78], and Michael–aza-Henry reactions [79]. They catalyzed the key asymmetric step leading to the natural product (*R*)-rolipram [77c, 80]. Catalyst **9e** promoted a Michael addition–decarboxylation process [80]. Hiemstra and coworkers chose a different access point on the chiral scaffold to synthesize their cinchona thiourea catalysts **11**, resulting in an altered catalytic cleft. Compound **11** was proven to catalyze Henry reactions [81]. Scheidt and coworkers applied the same catalyst in the stereoselective synthesis of flavanones and chromanones [82]. As a rare example, catalyst epi-**9d** with a naturally occurring C8–C9 stereochemistry was found to promote some Michael additions [83].

Cinchona alkaloid based thiourea catalysts have a tertiary amine basic function and an H-bond donor thiourea group. Based on the similar functional groups that these cinchona thiourea derivatives and Takemoto's catalyst share, their catalytic properties were expected to be analogous. Note that the scope of reactions promoted by the two catalyst classes is very similar, suggesting closely related modes of action. Furthermore, Pápai and coworkers extended their theoretical investigations of Takemoto's catalyst to quinine based derivative **9a** with parallel results [46]. Therefore, the manner of activation and substrate binding introduced in the previous section is likely to also apply to this catalyst class. Multifunctional organocatalysts bear several functional groups within one molecule. Some of them can establish H-bonds with each other, which can lead to self-association. According to NMR measurements catalyst **9a** exists mainly as a dimer in solution at lower temperatures, which is held together by intermolecular H-bonding and edge-to-face π–π stacking interactions (Figure 12.5) [84]. Song and coworkers demonstrated that association is a general concern with tertiary amine-thiourea catalysts [85]. They reported that above a certain concentration the selectivity of a catalyst started to drop with increasing loading. This phenomenon implies that dimers (or higher forms of association) have catalytic properties that are distinct from

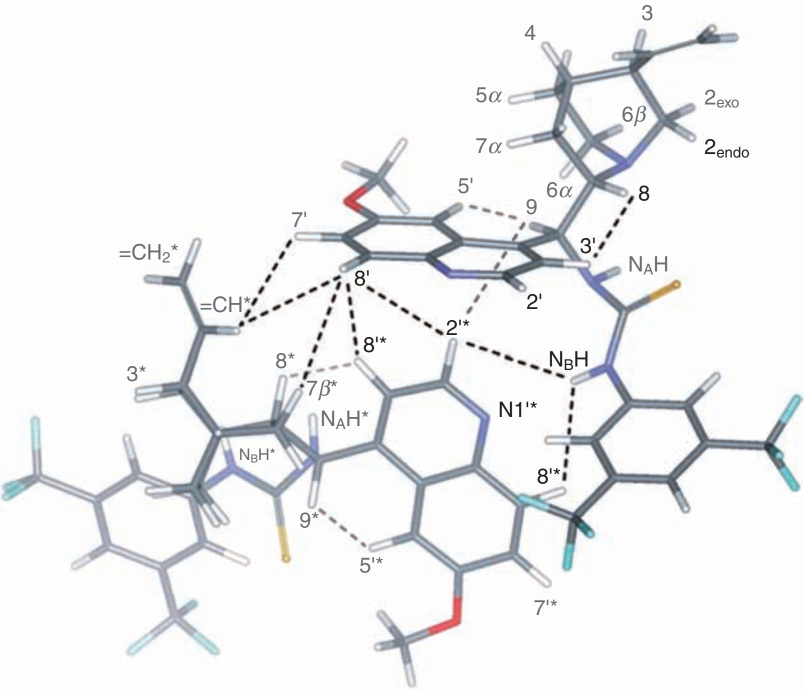
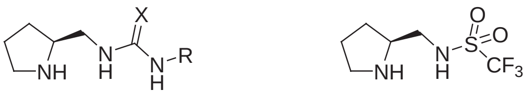


Figure 12.5 Dimeric structure of **9a** [84a]. The characteristic NOE contacts are indicated by dashed lines. The asterisk (*) is used to distinguish assignments in the "south" part of the dimeric assembly.

monomeric species. Therefore, the self-association aptitude of multifunctional organocatalysts must be taken into consideration when optimizing reaction conditions. Temperature and solvent polarity can greatly affect the association–dissociation equilibrium. Catalyst **9a** has been found to have optimal performance when its initial concentration is around 0.002 M (room temperature, toluene). As demonstrated, self-association lowers the concentration of the monomeric catalyst form, resulting in supramolecular structures with diminished or altered reactivity.

12.2.3
Pyrrolidine-(thio)urea Catalysis

L-Proline is a readily available chiral scaffold often involved in organocatalysis. Tang and coworkers synthesized the first pyrrolidine-(thio)urea derivatives **12a**,**b** (Figure 12.6) starting from L-proline in a couple of convenient steps to combine secondary amine and H-bond donor (thio)urea functions [27]. The features of proline catalysis have been extensively discussed in Chapter 1. The mode of action observed there is cardinally different from that of the cinchona alkaloid derivatives or Takemoto's catalyst. In the so-called enamine–iminium activation the catalyst covalently binds the carbonyl group of a substrate, instead of operating only with weak H-bonding interactions. Furthermore, secondary amine catalysts usually require Brønsted acid type additives (e.g., benzoic acid, *n*-butyric acid) for optimal performance. The difference between the two approaches is easily demonstrated by their efficiency in water. Often in non-covalent catalysis, water and other solvents capable of disturbing the H-bonds between catalyst and substrate have a strong negative effect on selectivity and in most cases on activity as well. Notable exceptions are Diels–Alder reactions (see above) and epoxide openings with **3a** that are even faster in water than in organic solvents, leading to the concept of hydrophobic amplification [25c]. Pyrrolidine-thiourea catalysts **12b–f** performed well in the Michael addition of cyclohexanone to nitroolefins in water, as reported by Xiao and coworkers [86]. Note that no conversion was observed in MeOH [87]. Despite



12 **13**

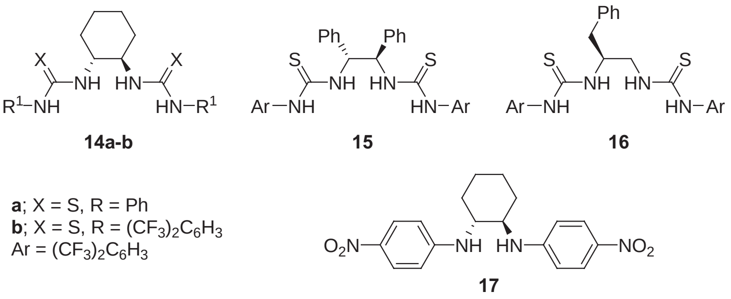
a; X = O, R = $(CF_3)_2C_6H_3$
b; X = S, R = $(CF_3)_2C_6H_3$
c; X = S, R = 4-Me-C_6H_4
d; X = S, R = *tert*-butyl
e; X = S, R = cyclohexyl
f; X = S, R = 1-naphthyl

Figure 12.6 Pyrrolidine-(thio)urea derivatives in organocatalysis.

the great difference in acidic strengths (**12b**, pK_a = 13.38; **12e**, p$K_a \approx 20$, in DMSO) [13b], which obviously influence H-bond donor abilities of the thiourea groups, these catalysts exhibit similar activity and selectivity (**12b**, 94% yield, 95 : 5 dr, 91% ee; **12e**, 87% yield, 94 : 6 dr, 90% ee). This observation suggests that H-bonding interactions play an auxiliary role compared to the covalent activation provided by the secondary amine group. However, the presence of a (thio)urea group is still favorable, as was demonstrated in a similar Michael–Michael tandem reaction [88]; various L-proline based organocatalysts were tested in polar protic media. The reaction was promoted with high conversion (99%) and selectivity (96% ee) exclusively when catalyst **12b** containing a secondary amine and a thiourea group was applied. Several L-proline derivatives were screened in the Michael addition of ketones to alkylide malonates [89]. Monodentate catalyst **13** proved to be the most efficient in this transformation, demonstrating that double H-bonding interactions may not always be essential.

12.2.4
Nagasawa's Catalyst

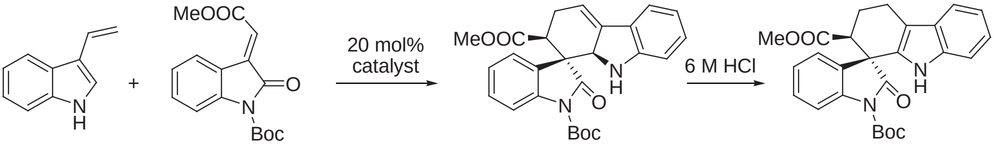
Bifunctional catalysis is not necessarily achieved by different functional groups, and an appropriate alignment of two identical groups in one molecule can also induce synergistic activation, especially when the "C_2-trick" – common in organometallic catalysis – is employed [90]. Nagasawa and coworkers examined the Baylis–Hillman reaction of cyclohexenone with various aldehydes and found that thiourea derivative **3a** significantly enhanced the reaction rates in the presence of organic bases. ^{1}H NMR measurements indicated that both substrates showed affinity to the catalyst, and a molecule bearing two thiourea binding sites was expected to interact simultaneously with both of them. Indeed, in the reaction of benzaldehyde with cyclohexenone catalyst **14b** (Figure 12.7) exhibited 72-fold rate enhancement compared to the uncatalyzed route, which was even slightly higher than that of thiourea **3a** (60-fold) [91]. Furthermore, moderate stereocontrol was observed (33% ee). Different chiral scaffolds were tested (Figure 12.7) to improve the selectivity, but *trans*-1,2-diaminocyclohexane remained the most effective



a; X = S, R = Ph
b; X = S, R = $(CF_3)_2C_6H_3$
Ar = $(CF_3)_2C_6H_3$

Figure 12.7 Homo-bifunctional catalyst candidates.

chiral backbone. Catalyst **14b** favored formation of the (*R*)-product, which is in line with the NMR observations that complexation, resulting in spectral changes, exclusively occurs between the catalyst and the (*R*)-enantiomer product. Despite the narrow substrate scope, as only sterically hindered aldehydes (e.g., cyclohexylcarbaldehyde, 72% yield, 90% ee) gave satisfactory results [91, 92], the viability of acid–acid bifunctional organocatalysis was successfully demonstrated. Later, several applications of the same catalyst were presented: asymmetric Wittig reaction [93], Diels–Alder reaction [94], kinetic resolution of amines [95], and the Mannich reaction of phosphorous ylides [96]. An outstanding asymmetric catalytic process, the Diels–Alder reaction of 3-vinylindoles and methylene-indolinones, was selected to demonstrate the modes of action of catalyst **14b** (Scheme 12.2) [94].



18 **19** **20** **21**

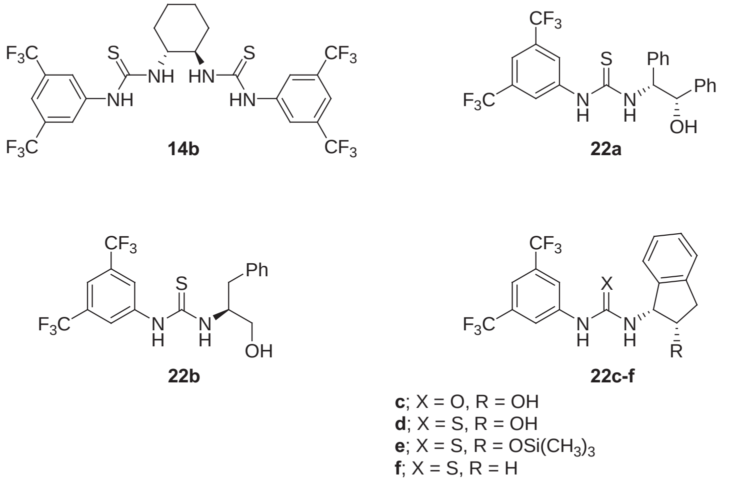
99% yield, >99:1 dr, 96% ee

Scheme 12.2 Selected example of a highly stereoselective Diels–Alder reaction [94].

Barbas and coworkers reported excellent yields and selectivities for a broad spectrum of derivatives in a reaction creating several stereogenic centers (99–89% yield, >99 : 1 dr, 97–88% ee). H-bond donor ability was found to be essential for high enantioselectivity: catalyst **14b** (pK_a = 11.98 in DMSO) [13b] promoted the reaction in toluene with 75% ee, while catalyst **14a** (pK_a ~ 13.5 in DMSO) [13b] exhibited only 42% ee with similar activity and diastereoselectivity. Note that the reaction showed strong solvent dependence, owing to the weak H-bonding interactions between catalyst and substrates. Accordingly, the highest selectivity was achieved in hexanes (>99 : 1 dr, 99% ee), whereas methanol removed it completely (3.5 : 1 dr, 0% ee). Detailed investigations were undertaken to reveal the mechanism of the reaction and the source of this rare selectivity. Interactions were detected between catalyst **14b** and methylene-indolinone **19** in the ^{13}C NMR spectra, as the signals of the substrate shifted downfield (up to 0.98 ppm). In contrast, no such complexation was found with substrate **18**, suggesting a subsequent admission of **18** to the catalyst–**19** adduct. Furthermore, almost complete loss of selectivity was observed when either **18** was *N*-methylated or when the Boc protecting group was replaced in **19** with H or a benzyl group. This implies an H-bonding interaction between the aforementioned groups and an active contribution of the substrates to their orientation prior to C–C bond formation. Note that this transformation is also attractive from a practical point of view: the products were separated from the reaction mixture via filtration, the catalyst solution was applied in several subsequent cycles without significant loss of activity or selectivity, reaction times were generally under 10 min, and the reaction appeared to be scalable.

12.2.5
Ricci's Thiourea Catalyst

Inspired by the performance of (thio)urea **3a**,**b** catalysts in Friedel–Crafts reactions [19] Ricci and coworkers introduced the asymmetric addition of indoles to nitroolefins in 2005 [97], using various catalysts with the double H-bond donor (thio)urea moiety (Figure 12.8). Homo-bifunctional catalyst **14b** proved to be ineffective in terms of activity and selectivity in the addition of indole to nitrostyrene (toluene, 40% conv., 7% ee). Replacing one of the thiourea moieties with an amphoteric OH group, capable of both donating and accepting H-bonds, led to somewhat better results. The most promising of these candidates was compound **22d** (toluene, >95% conv., 35% ee). The necessity of one sufficiently acidic (thio)urea group was demonstrated by the inferior performance of urea derivative **22c** (toluene, 23% conv., 25% ee). Note that **22d** has a pK_a of 12.98, where **22c** has a pK_a of 17.63 in DMSO [13b]. The reaction temperature and the solvent had a strong influence on selectivity; optimized conditions (–24 °C, DCM) provided high ee values without sacrificing catalyst activity (**22d**, 92% conv., 85% ee). To gain mechanistic insight into the mode of activation, a series of control experiments was conducted. It was found that the presence of the OH group is essential to catalytic efficiency, since both **22e** (18% yield, 39% ee) and **22f** (15% yield, 0% ee) showed poor performance. This implies a bifunctional mode of action through a synergistic activation of indole and nitrostyrene substrates (Figure 12.9). Accordingly, the loss of the N–H group in *N*-methylindole as a substrate disturbs the stereocontrol of the process, resulting in practically racemic product under optimized conditions (75% yield, 6% ee). Ricci's thiourea catalyst was later applied in several reactions. In the same transformation as that of the proof-of-principle study



14b

22a

22b

22c-f

c; X = O, R = OH
d; X = S, R = OH
e; X = S, R = OSi(CH$_3$)$_3$
f; X = S, R = H

Figure 12.8 Catalysts tested in the Friedel–Crafts reaction of indoles with nitroalkenes.

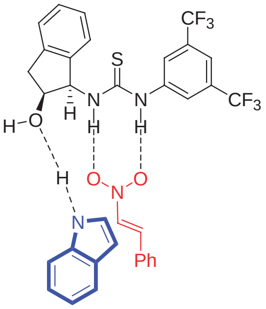
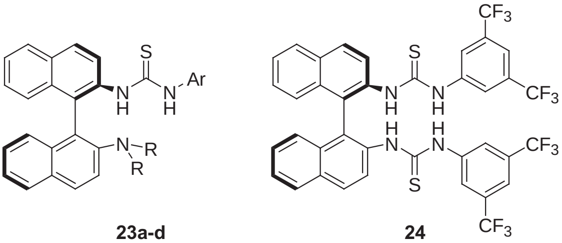


Figure 12.9 Plausible mode of activation of catalyst **22d** [97].



23a-d **24**

a; R = Me, Ar = 3,5-$(CF_3)_2C_6H_3$
b; R = Et, Ar = 3,5-$(CF_3)_2C_6H_3$
c; R = Me, Ar = 4-Cl-C_6H_4
d; R = H, Ar = 3,5-$(CF_3)_2C_6H_3$

Figure 12.10 Axial chiral thiourea derivatives.

several Brønsted acids were used to improve the outcome through co-operative catalysis (mandelic acid was the additive of choice) [25d, 98]. The Friedel–Crafts reaction of indoles with unsaturated phosphonates [67a], Michael addition of formaldehyde *N*,*N*-dialkylhydrazones to β,γ-unsaturated α-keto esters [99], and conjugate amine (aza-Michael) additions [100] were carried out with catalyst **22d** or its enantiomer. Similarly to cinchona thiourea derivatives, the epimerization of only one catalytically involved stereogenic center in **22d** leads to poor performance [100]. In other words, the *cis* orientation of the thiourea and the OH group is a prerequisite to successful bifunctional activation in the current system.

12.2.6
Binaphthylamine Scaffolds in (Thio)urea Catalysis

Most of the chiral scaffolds presented in this chapter contain at least one stereogenic center, which creates the necessary asymmetric environment for chiral catalysis. Wang and coworkers chose a slightly different approach when introducing axially chiral catalyst **23a** (Figure 12.10) [101]. This binaphthyl amine based compound bears a basic tertiary amine group and a double H-bond donor thiourea moiety. Owing to its similar functional groups, catalyst **23a** was expected to act similarly to Takemoto's catalyst **4e** and cinchona thiourea derivatives (Figure 12.4). Therefore, the Michael addition of acetyl acetone to nitroolefins was chosen to compare catalytic performances. Wang's thiourea catalyst exhibited superior activity and selectivity, which was preserved even at only 1% catalyst loading (95% yield, 95% ee). This rare activity can be rationalized by the increased acidic strength of **23a** ($pK_a = 10.72$ in DMSO) [13b] compared to other chiral thiourea representatives, leading to stronger H-bond donor ability.

The same catalyst was applied in the Morita–Baylis–Hillman reaction of cyclohexenone and various aldehydes [102]. Takemoto's catalyst **4e** and two closely related derivatives **23b,c** were tested for comparison to establish structure–reactivity relations. According to our current knowledge regarding the mechanism of the Morita–Baylis–Hillman reaction [103], the first step is a Michael-type addition of the tertiary amine group to cyclohexenone. Therefore, increased steric bulk around the basic nitrogen reduces the activity of the catalyst in the model reaction (**23a**, 83% yield, 71% ee; **23b**, 56% yield, 73% ee). Note that the selectivity is not affected by this change. In contrast, replacing the strongly electron-withdrawing 3,5-bis(trifluoromethyl)phenyl with a 4-chlorophenyl group in **23c** renders the catalyst practically inactive (18% yield). This could be explained by the lower acidic strength of the thiourea group leading to weaker H-bonding ability [17]. Takemoto's catalyst is a remarkably weaker acid than **23a** based on their pK_a values, and a similar loss of activity and selectivity was observed in this case (**4e**, 21% yield, 39% ee) [13b]. Optimized reaction conditions involve acetonitrile as solvent and a reaction temperature of 0 °C. This protocol turned out to be generally applicable to a wide range of aldehydes, furnishing products with good yields and selectivities (63–84% yield, 80–94% ee). Note that aromatic 2-chlorobenzaldehyde proved to be a less suitable substrate (55% yield, 60% ee).

In 2009 primary amine catalysis was successfully combined with this thiourea catalyst family: the Michael addition of oxindoles to α,β-unsaturated aldehydes was promoted by catalyst **23d**. Two stereogenic centers were created with good selectivity in a single step [104]. It was earlier demonstrated that homo-bifunctional catalysts bearing multiple identical functional groups can promote suitable reactions (see 12.2.4). Binaphthyl amine thiourea derivative **24** was identified in careful structure optimization studies as the catalyst of choice in some Friedel–Crafts [105] and aza-Henry reactions [106]. Increasing the H-bond donating ability implemented by various substituents on the thiourea group corresponded well with the observed activity and selectivity of the catalyst.

12.2.7
Jacobsen's Catalyst Family

During the usual course of catalyst development several closely related candidates are synthesized and evaluated. In this way certain structural changes with beneficial effect on catalysis can be identified, and incorporated in the final catalyst.

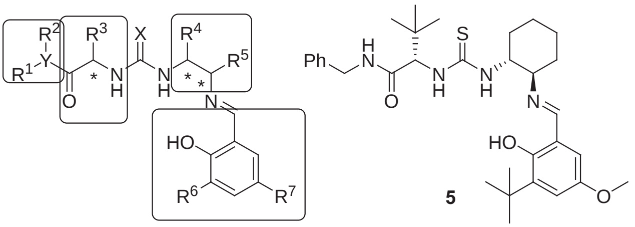


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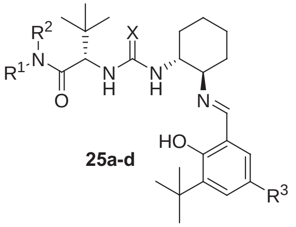
Figure 12.11 Combinatorial approach to catalyst structure optimization.

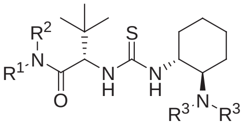
Depending on the chiral scaffold in use different levels of optimization are needed. For chiral pool scaffolds (e.g., cinchona alkaloids) a thorough investigation of the optimal orientation and identity of all functions is neither necessary nor possible. A truly modular synthetic route makes it easy to create a catalyst library, but lacks an initial lead molecule. This approach requires a great number of candidates, especially in the case of multifunctional catalysts, where the catalytic efficiency is a result of several structural features. Jacobsen and coworkers have provided a textbook example of catalyst structure optimization in the asymmetric Strecker reaction [26]. They were originally looking for chiral ligands for metal catalysis, but the best selectivity was achieved by the organic ligand in the absence of metals (19% ee). The structure of the catalyst offers various access points for modifications (Figure 12.11). The identity of the amino acid (naturally occurring or artificial) along with its relative configuration to the diamine moiety exhibited a strong influence on catalytic performance. Thiourea derivatives (X = S) were generally better than ureas (X = O), and substituents on the salicylaldehyde (R^6, R^7) also influenced the stereochemical outcome. The screening was carried out with catalyst candidates immobilized on solid support. The most promising compounds, however, were synthesized and applied as homogeneous catalysts. The viability of this combinatorial optimization approach is easily demonstrated by the performance of the final catalyst it yielded (**5:** 91% ee in the given reaction).

Since the introduction of the catalyst family several derivatives have been prepared to widen the scope of reaction types promoted by one of them (for selected examples see Figure 12.12). Note that structurally the closer two catalyst are the more similar the behavior they exhibit. The applications listed below are optimally, but not exclusively, promoted by the indicated derivative. Catalyst **25a** was effective in hydrophosphonylation reactions [107] and the acylcyanation of imines [108]. Three-component acyl-Strecker reactions [109], and this derivative was applied in the total syntheses of (*R*)-(−)-calycotomine, (*S*)-(−)-salsolidine, and (*S*)-(−)-carnegine [110]. Catalyst **25b** promoted some Mannich [111] and aza-Baylis–Hillman [112] reactions. Catalyst **26a** accomplished cyanosilylation reactions of ketones [113], and was involved in the syntheses of hydroxy wilfordic acid [114] and Bengazole analogs [115]. Catalyst **26b** promoted direct conjugate additions of ketones to nitroalkenes [116], while catalyst **26c** gave the best results in direct conjugate additions of aldehydes to nitroalkenes [117]. Catalyst **26d** promoted the dynamic kinetic resolution of azlactones [118], the kinetic resolution of oxazinones [119],



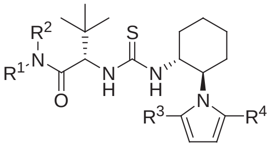
25a-d

a; R^1 = Me, R^2 = Me, R^3 = OCO*t*Bu, X = S
b; R^1 = Bn, R^2 = Me, R^3 = *t*Bu, X = S
c; R^1 = Bn, R^2 = H, R^3 = OCO*t*Bu, X = O
d; R^1 = Bn, R^2 = Me, R^3 = OCO*t*Bu, X = S



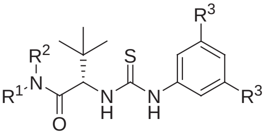
26a-d

a; R^1 = H, R^2 = Me, R^3 = *n*-Pr
b; R^1 = Bn, R^2 = Me, R^3 = H
c; R^1 = Bn, R^2 = H, R^3 = H
d; R^1 = Bn, R^2 = Me, R^3 = Me



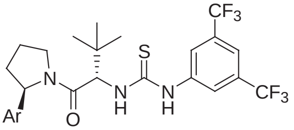
27a-c

a; R^1 = *i*-Bu, R^2 = *i*-Bu, R^3 = Me, R^4 = Ph
b; R^1 = *n*-pentyl, R^2 = Me, R^3 = Me, R^4 = Ph
c; R^1 = Et, R^2 = Et, R^3 = Me, R^4 = Me



28a-c

a; R^1 = Me, R^2 = CH(Ph)$_2$, R^3 = CF$_3$
b; R^1 = Me, R^2 = Bn, R^3 = CF$_3$
c; R^1 = Me, R^2 = Bn, R^3 = H



29a-c

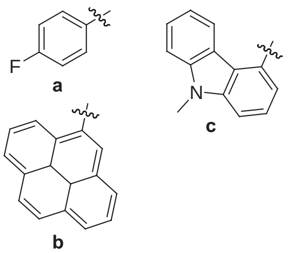
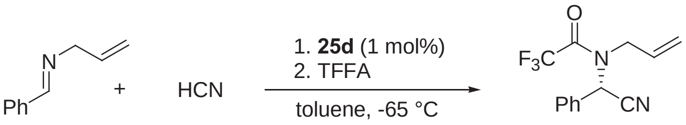


Figure 12.12 Selected examples from the Jacobsen catalyst family.

and nucleophilic additions to imines [120]. Catalyst **27a** promoted acyl-Pictet–Spengler reactions [121] and the acyl-Mannich reaction of isoquinolines [122]. It was also employed in the total synthesis of (+)-yohimbine (11 steps, 14% overall yield) [123]. Catalyst **27b** proved to be effective in Pictet–Spengler cyclization reactions [124] and the total synthesis of (+)-harmicine [124]. The slightly modified derivative **27c** developed by List and coworkers catalyzed the transfer hydrogenation of nitroolefins [125] and nitroacrylates [126]. Catalyst **28a** gave access to a broad spectrum of amino acids with good overall yields and excellent selectivities through a Strecker reaction as the key asymmetric step. Furthermore, the multigram scale of the reactions, low catalyst loading (0.5%), and ambient temperature (0 °C) made the process attractive from a practical viewpoint [127]. The same catalyst was applied in *iso*-Pictet–Spengler reactions [128]. Catalyst **28b** promoted the addition reaction of *β*-keto benzothiazole-sulfones to *N*-Boc-protected imines [129], the formal aza-Michael addition of ammonia to nitroalkenes [130], and Steglich rearrangements [131]. Catalysts **29a–c** promoted addition reactions to oxocarbenium ions [132], cationic polycyclizations [133], and the reaction of silyl ketene acetals with acyl fluorides [134], respectively.

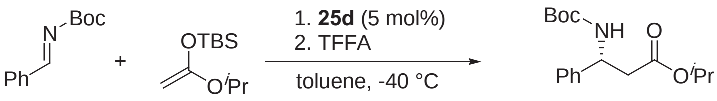
Parallel to catalyst development and a search for new applications the Jacobsen group set out to elucidate the mode of action of this potent catalyst class. Detailed NMR investigations revealed a well-defined secondary structure of representative **25c** in solution. This catalyst gave excellent results in Strecker reactions and various imines were chosen to study the effect of complexation on catalyst conformation. No significant change in the secondary structure was observed upon binding with the substrate [135], suggesting that **25c** adopts a nearly favorable conformation for catalysis in its free form. Non-covalent organocatalysts operate with weak H-bonds, making it otherwise difficult to overcome entropy loss when the substrate docks. The urea group was identified as the only catalytically relevant H-bond donor group; alkylation of the phenolic or the amide proton had practically no effect on activity, whereas modifications to the urea moiety were detrimental. In another study catalyst **25d** was the subject of investigation. Although this compound promoted both Strecker and Mannich reactions of imines (Scheme 12.3) the great differences in substrates implied distinctly different reaction mechanisms. For instance, modifications to the salicylimine moiety had a significant impact on the outcome of the Strecker reaction, while having practically no affect on the Mannich reaction. Furthermore, the Mannich reaction was indifferent to the relative configuration of the diamino cyclohexyl group. This observation led to

Strecker reaction



30 **31** **32**

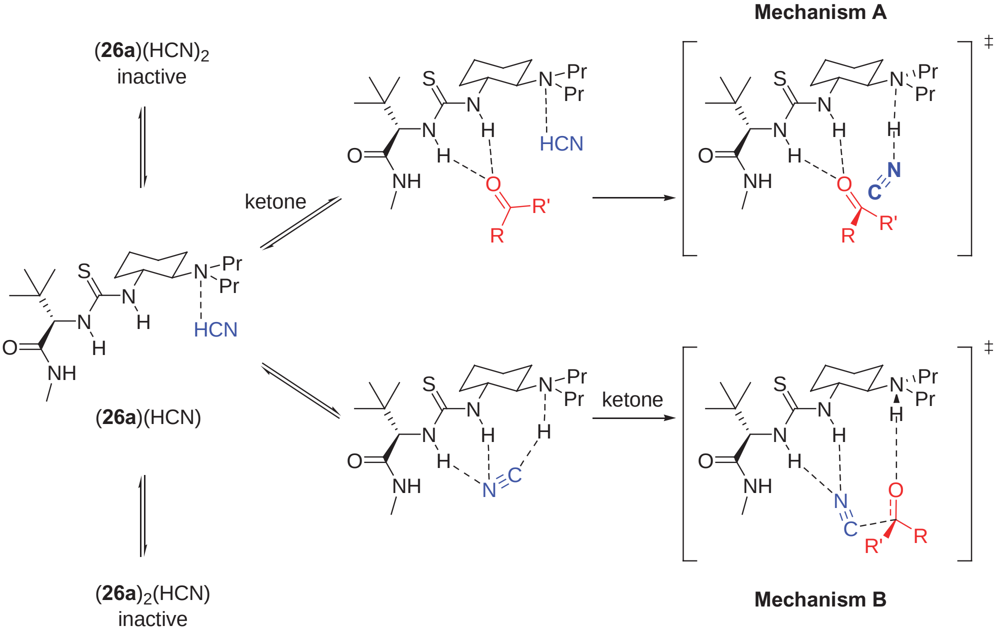
Mannich reaction



33 **34** **35**

Scheme 12.3 Strecker and Mannich reactions of imines [136].

a simplified design containing only one stereogenic center in the amino acid building block, but preserving excellent catalytic performance (**28c**, 100% conv., 94% ee) [136]. Structure–reactivity relations concerning a wide range of modifications on catalyst structure were established through the large number of derivatives synthesized and tested. However, detailed mechanistic understanding of these catalysts was still not presented. The cyanosilylation reaction of ketones promoted by catalyst **26a** was extensively studied by kinetic measurements and DFT computations [137]. Experimental data pointed to a ternary catalyst–HCN–ketone transition state complex, and a bifunctional involvement of the catalyst (Scheme 12.4). Computations identified mechanism A as the favorable (by 4.7 kcal mol^{-1}) reaction pathway, where the carbonyl oxygen of the substrate is supported by clamp-like double H-bonds from the thiourea group.



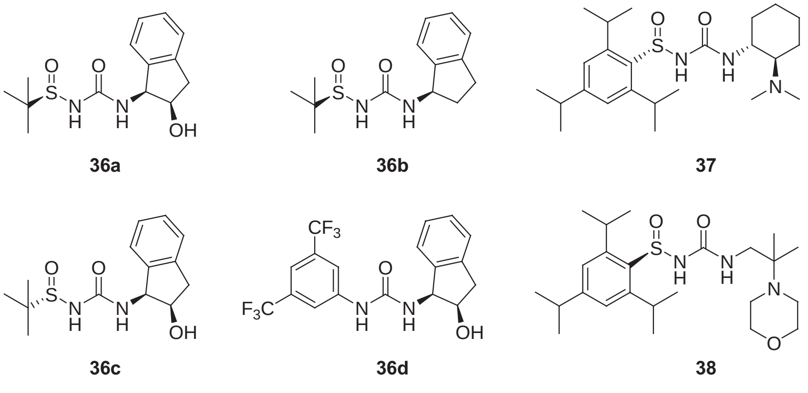
Scheme 12.4 Proposed mechanism of the cyanosilylation reaction of ketones [137].

The high selectivity observed in these reactions was achieved at cryogenic temperatures, suggesting weak catalyst–substrate interactions that are unable to suppress background reactions at higher temperatures. This can be ascribed to the limited H-bond donor ability of (thio)urea groups, originating from weak N–H acidity (**27c**, $pK_a = 19.6$; **25b**, $pK_a \approx 18.3$, in DMSO) [13b]. Modifications of the catalyst structure, including the introduction of a 3,5-bis(trifluoromethyl)phenyl group in catalyst **28a** ($pK_a = 12.57$ in DMSO) [13b], resulted in efficient asymmetric reaction control at a significantly higher temperature (0 °C) [127].

12.2.8
N-Sulfinyl (Thio)urea Catalysts

In previous examples, the (thio)urea subunit of a catalyst was either connected to an electron-withdrawing group [typically a 3,5-bis(trifluoromethyl)phenyl group] to enhance its H-bond donor ability or it bore two chiral substituents, allowing better stereocontrol in certain reactions. The latter design also offered greater room for optimization, which was fully exploited by Jacobsen and coworkers in their early set of catalysts [26]. In an attempt to combine these two structural features that (thio)urea catalysts formerly did not share, the *N*-sulfinyl group was introduced by Ellman and coworkers [138]. It has a significant acidifying effect on the adjacent (thio)urea moiety and serves as an additional stereogenic center. Careful optimization led to structure **36a** (Figure 12.13), which proved to be the catalyst of choice in the aza-Henry reaction of Boc-benzaldimine and nitroethane (99% conv., 83 : 17 dr, 94% ee). The loss of the hydroxyl function was detrimental to enantioselectivity (**36b**, 99% conv., 21 : 79 dr, 0% ee); an inversion of the stereochemistry around the sulfur atom (**36c**, 90% conv., 71 : 29 dr, 80% ee) or replacement of the *N*-sulfinyl moiety with a 3,5-bis(trifluoromethyl)phenyl group (**36d**, 82% conv., 83 : 17 dr, 80% ee) resulted in slightly inferior catalysts. Note that compound **36d** is the enantiomer of Ricci's urea catalyst **22c**. The reaction tolerated a wide variety of substrates. For the first time, aliphatic imines were transformed into the corresponding aza-Henry products with high selectivity. This study once again underlines that the type of functional groups and their spatial alignment together determine the performance of a catalyst.

New applications demanded changes in catalyst structure. The steric bulk around the sulfur atom was increased and a tertiary amine function was introduced on a cyclohexyl framework in catalyst **37** to efficiently promote the addition reactions of thioacetic acid to nitroalkenes [139]. The general procedure developed here was applied as the key asymmetric step in the synthesis of (*R*)-sulconazole (32% overall yield for five steps, 96% ee). A very similar catalyst was used in the



36a **36b** **37**

36c **36d** **38**

Figure 12.13 *N*-Sulfinyl urea catalysts.

addition reactions of a Meldrum's acid derivative to nitroalkenes, which provided convenient access to γ-amino acids [140]. The viability of this reaction as a practical method was demonstrated by the 1 molar scale synthesis of the drug (*S*)-pregabalin (Lyrica) with a catalyst loading as low as 0.2 mol%. High selectivity can be achieved in the reactions of α-substituted Meldrum's acids and α-substituted nitroalkenes with a catalyst only chiral at the sulfinyl group (**38**) [141]. The products obtained in these reactions were transformed into α,γ-disubstituted γ-lactams in a straightforward two-step procedure.

12.3
Summary

(Thio)urea organocatalysis has emerged from the observation that a double H-bond donor moiety in close proximity and proper orientation can bind simultaneously to the same H-bond acceptor of a substrate. The double H-bonding interaction is superior to monodentate binding and leads to enhanced recognition and transition state (often oxyanion-type) stabilization. The strength of the H-bond provided by the (thio)urea moiety can readily be fine-tuned through substitution that alters the polarity of the thiourea N–H bonds. As a result, (thio)urea organocatalysts have pK_a values in the range of 8.5–20, spanning 12 orders of magnitudes. In most cases reaction control is achieved exclusively by non-covalent interactions between the catalyst and substrates, and product inhibition is rare. The (thio)urea group can readily be combined with other functionalities, resulting in cooperative or bifunctional catalysis. Cooperative catalysis means that certain additives (e.g., Brønsted acids) have a beneficial effect on catalyst performance, while bifunctional catalysts imply synergistic activation of multiple substrates by catalytically active moieties incorporated within the same molecule. Careful optimization of the catalyst structure and the strength of H-bonds provided by the (thio)urea moiety leads to excellent activity (low catalyst loading) and selectivity (even at ambient temperatures). This tunability together with their generally easy and convenient syntheses makes (thio)urea organocatalysts particularly attractive from a practical viewpoint. Several natural products and important chiral building blocks have been synthesized with the aid of (thio)urea derivatives. This rapidly growing catalyst family is one of the most versatile in asymmetric organocatalysis.

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13
Brønsted Bases

Amal Ting and Scott E. Schaus

13.1
Introduction

As an essential component to asymmetric organocatalysis, chiral, metal-free Brønsted bases have mediated several types of C–C and C–X bond-forming reactions mediated by enamine and enolates. Brønsted bases (Figure 13.1) have the functional capacity to accept a hydrogen (or proton) from an acidic source or equivalent activated species. This proton transfer forms the basis of the key activation component to new-bond formation reactions.

Early Brønsted bases performed the task of promoting carbon–carbon and carbon–heteroatom formation in unselective manners. The basis of asymmetric control in a reaction was largely attributed to chiral metal-containing Lewis acids for some time. Over the last two decades, organocatalysis has shifted focus towards chiral organic molecules where hydrogen and nitrogen moieties of a Brønsted base, including the sterics of such catalysts, offer exclusive control over the stereoselectivity of a reaction transformation [1].

The mechanistic role played by Brønsted bases involves either a pro-nucleophile or a stabilized, charged nucleophile–electrophile adduct; both species lose a proton to the amine moiety of the Brønsted base, resulting in newly activated intermediates with basic character (Figure 13.1). The activated intermediate species during the course of the reaction are involved in a second proton transfer event from the protonated Brønsted base, which frees up the Brønsted base for subsequent cycles of activity.

The intrinsic nature of the ion pairing complex of Brønsted bases can become a challenge when stereoinduction comes into play, especially when the starting reagents are achiral. Catalysts that combine both a Brønsted base moiety and another site with hydrogen-donating characteristics provide a bifunctional Brønsted catalyst that can overcome the stereoinduction issues. In such way, the Brønsted catalyst has the ability to stabilize both nucleophile and electrophiles in the transition state. As a result, better catalysts are designed to obtain such stabilized activation states (Figure 13.2).

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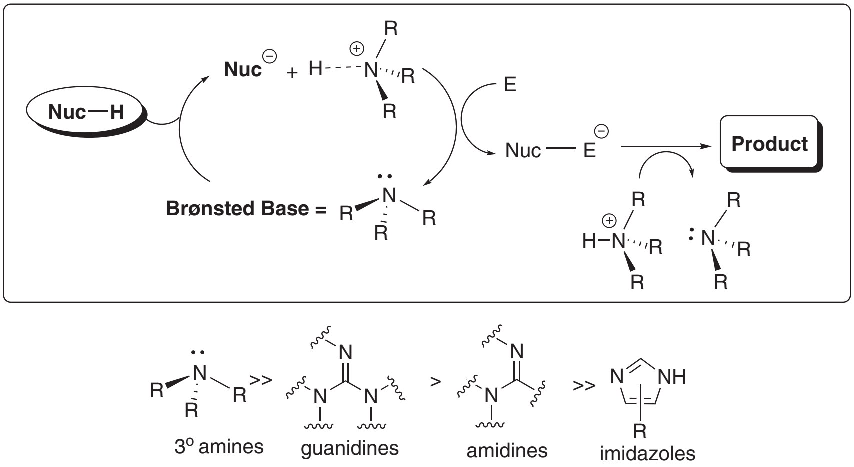


Figure 13.1 Brønsted basic nitrogens utilized in chiral organocatalysis.

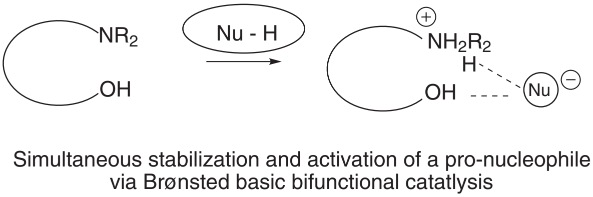

NR₂
OH
Nu - H
NH₂R₂⊕
H
OH
Nu⊖
Simultaneous stabilization and activation of a pro-nucleophile
via Brønsted basic bifunctional catatlysis

Figure 13.2 Pronucleophile activation under bifunctional Brønsted base catalysis.

In this chapter, bifunctional Brønsted base catalysts will also be addressed. Bifunctional catalysts are elegantly designed to activate *both* nucleophiles and electrophiles during the bond formation process. Notably, the catalyst's Brønsted base component is distinguished as a basic unit crucial for catalytic activity, involving a base-promoted proton abstraction as the activation step. These synthetic advances in mechanistic understanding and catalyst design have resulted in an increase in the versatility of new methodology development and synthetic transformations.

13.2
Cinchona Alkaloids

Chiral Brønsted base catalysis began with the recognition of a natural product class of compounds in the cinchona alkaloid family [2]. Cinchona alkaloids are templates for Brønsted bases when their quinuclidine nitrogen is protonated by nucleophilic substrates, resulting in a stabilized chiral intermediate for stereochemical attack of an electrophile. Systematic evaluation of structural variants to the scaffold

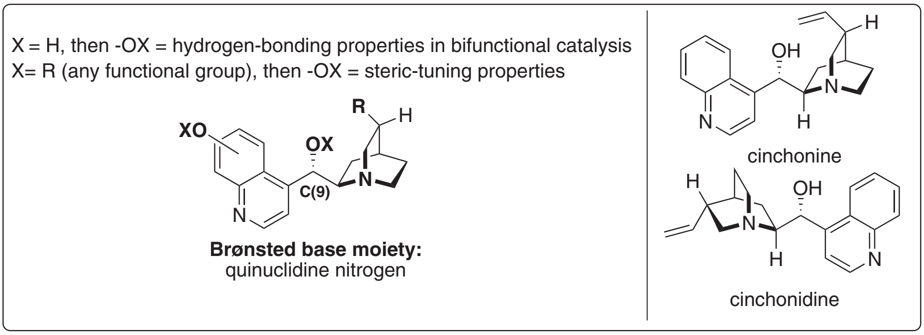

X = H, then -OX = hydrogen-bonding properties in bifunctional catalysis
X= R (any functional group), then -OX = steric-tuning properties
XO
OX
R
H
N
C(9)
N
Brønsted base moiety:
quinuclidine nitrogen
OH
H
N
N
H
cinchonine
H
OH
N
H
N
cinchonidine

Figure 13.3 Basic scaffold of cinchona alkaloids.

backbone has guided better understanding of the properties crucial for enantioselective catalysis [3]. The relative positioning of the rigid backbone with the basic quinuclidine moiety and also the option of having additional hydrogen-bond donors within the same catalyst structure are all highlighted components of the catalyst. Such insight into the catalyst scaffold has led to the synthesis of novel bifunctional cinchona alkaloid-based catalysts with modified hydrogen-bond donor capabilities and defined steric attributes (Figure 13.3). Such broadened scope in the utility for this class of catalysts reinforced the importance of understanding the bifunctional motif in Brønsted base catalysis.

13.2.1
Cinchona Alkaloids in Asymmetric Transformations

The unique role of cinchona alkaloids with their molecular recognition abilities for asymmetric synthesis is demonstrated by the vast number of natural and synthetic designs [4] The cinchona alkaloids, with quinine being its most well-known natural product, are complex molecules containing five stereogenic centers, a basic quinuclidine nitrogen, and a chiral secondary alcohol. Tailor-made functional groups added to the complex, yet flexible alkaloid scaffold enable this class of bifunctional Brønsted base catalysts for specific asymmetric applications. The first application of cinchona alkaloids as chiral promoters to a reaction have been reviewed by Pracejus [5], Morrison and Mosher [6], and Wynberg [7].

A highlighted advantage with cinchona alkaloid catalysis is the attainability of either enantiomer, as a result of the catalysts pseudo-enantiomeric pairs. Pseudo-enantiomeric alkaloids in the natural open conformation retain torsion angles opposite in sign: quinine and cinchonidine are (−), and thereby induce selectivity for one enantiomer, while quinidine and cinchonine are (+) and afford the other enantiomer [8]. Another class of cinchona alkaloids are the cupreines and cupreidines where replacement of quinoline C(6′)-OCH_3 with an OH-group confers bifunctional character to the catalyst. The availability of an additional hydrogen-bonding moiety offers stronger stereogenic-tuning to the activated, stabilized transition state, as illustrated in Figure 13.4.

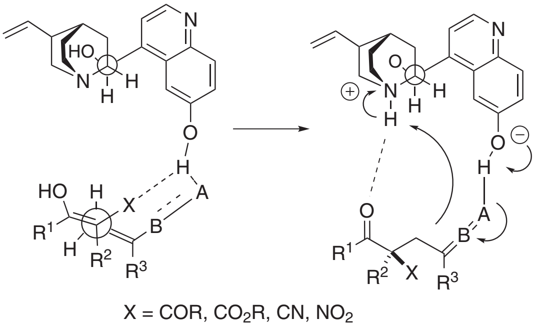


Figure 13.4 Asymmetric activation of conjugate additions via cinchona alkaloids.

This section focuses on the role of cinchona alkaloids as Brønsted bases in organocatalytic asymmetric reactions. Cinchona alkaloids may act in a Lewis basic manner when the quinuclidine nitrogen initiates a nucleophilic attack to the substrate in asymmetric reactions such as the Baylis–Hillman, asymmetric α-halogenation, and alkylation [9].

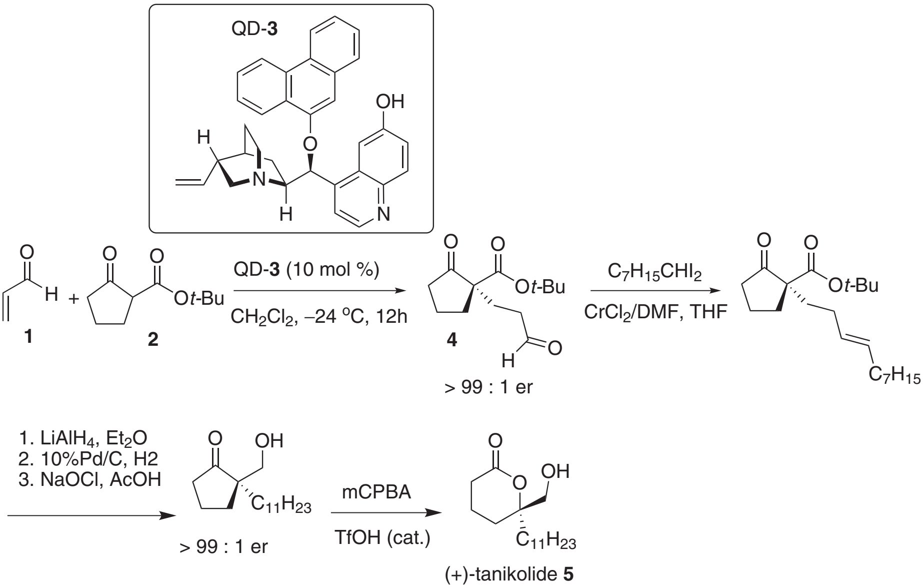
The more prominent role of cinchona alkaloids is their significance as Brønsted bases. Cinchona alkaloids are mechanistically categorized as Brønsted bases when the nitrogen moiety partially or fully activates a proton, resulting in the chiral intermediate species with facial selectivity in asymmetric catalysis. Modified cinchona alkaloid catalysts continuously evolve within the search to further improve the bifunctional mode and versatility of this Brønsted basic catalyst. Derivations at the C(9)-OH group, replacement of quinoline C(6′)-OR groups with hydrogen bonding moieties, syntheses of bis-cinchona alkaloids, and development of thiourea-derived cinchona alkaloids have become the early starting platforms for catalyst design.

The reactions discussed here highlight the utility of the catalyst, notably the design of the scaffold to achieve the desired stereoinduction with low catalyst loading while achieving high yields. These reactions are categorized as conjugate additions to enones or enoates, imines, azodicarboxylates, and nitroolefins.

13.2.2
Asymmetric Activation of Conjugate Addition to Enones

Michael donors and acceptors are common components in Brønsted base-mediated catalysis. Such transformations offer an uncomplicated route towards all-carbon quaternary stereocenters. In the most basic form, α,β-unsaturated aldehydes are highly reactive templates towards nucleophilic reactions. Under such conditions, mechanistic studies show no polymerization of the unsaturated aldehydes under cinchona alkaloid catalysis [10]. This absence of polymerization is a key mechanistic indicator that the quinuclidine nitrogen of the catalyst does not act as a nucleophilic promoter. Rather, the quinuclidine nitrogen acts, as predicted, in a Brønsted basic deprotonation–activation of various cyclic and acyclic

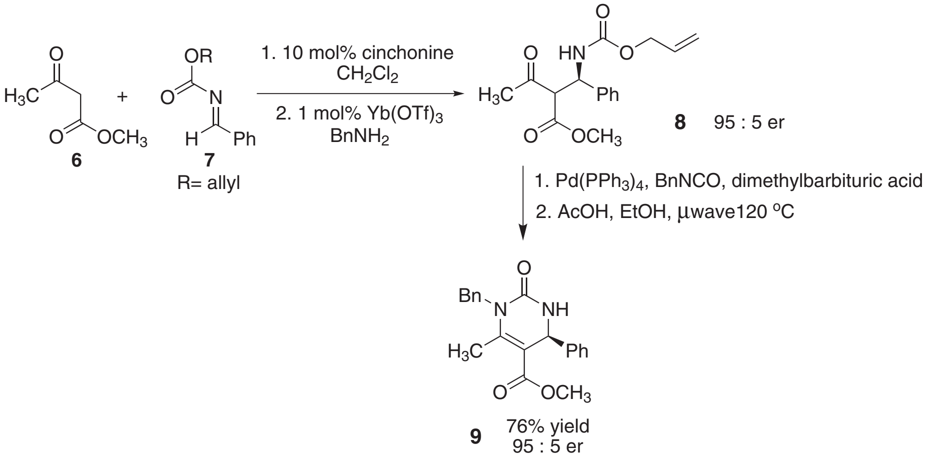
1,3-dicarbonyl donors. Consequently, the utility of this reaction was demonstrated by Deng and coworkers in the seven-step synthesis of (+)-tanikolide **5**, an antifungal metabolite (Scheme 13.1).



Scheme 13.1

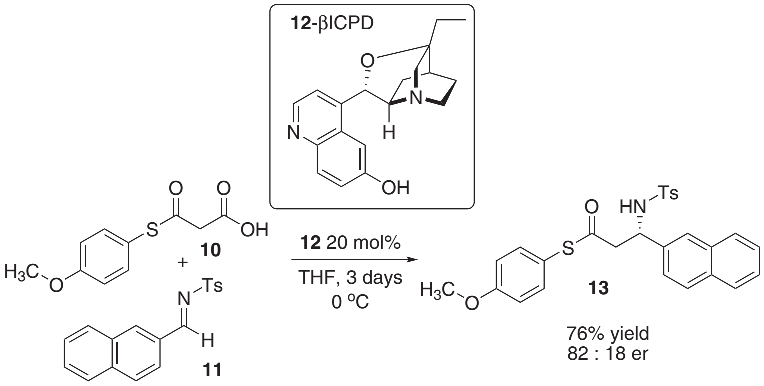
13.2.3
Asymmetric Activation of Conjugate Addition to Imines

Chiral secondary amine catalysts were the earliest examples of enantioselective organocatalytic Mannich reactions. This class of secondary amines catalysts, designed as functionalized prolines or pyrrolidines, generates reactive enamine or iminium intermediate species *in situ*, albeit under stoichiometric amounts of catalyst load [11]. In early applications of cinchona alkaloids, numerous works showed the efficiency of these catalysts in mediating aldol reactions of malonates or 1,3-dicarbonyls with significantly lower catalytic loadings than secondary amine catalysts [12]. The cinchona alkaloid catalyzed Mannich addition, employing the use of imines rather than aldehydes as the electrophile, was explored by a few groups [13]. The use of 1,3-dicarbonyls as pro-nucleophiles was first explored by Schaus and coworkers [13a] in the conjugate addition of β-ketoesters to *N*-acyl aldimines (Scheme 13.2). Using a low catalyst loading of 10 mol% cinchonine, highly enantioselective multifunctional secondary amine adducts were obtained. The creative utility of the optically pure Mannich product was shown in the subsequent conversion into chiral dihydropyrimidones (**9**) via two steps, offering a novel approach towards chiral 5-benzylpyrimidone scaffolds, in 96% yield and 95 : 5 er.



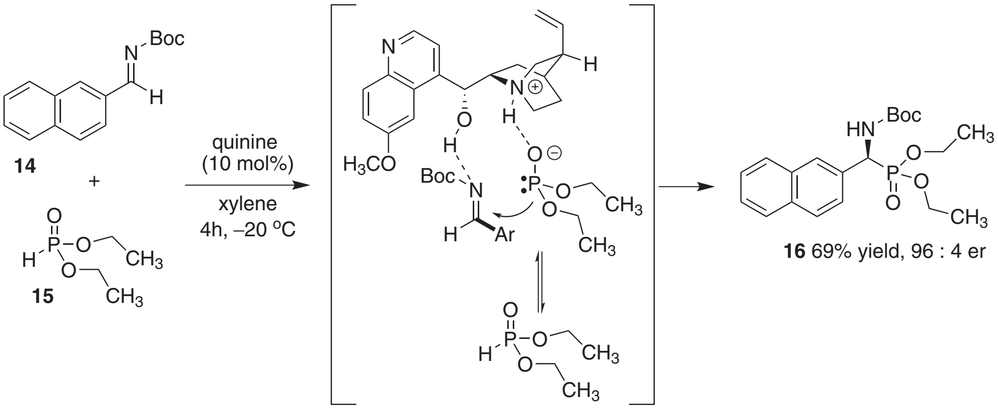
Scheme 13.2

1,3-Dicarbonyl donors can also undergo two tandem *in situ* activation steps mediated by cinchona alkaloids, as demonstrated by Ricci and coworkers (Scheme 13.3). [13c] In an enantioselective decarboxylative addition of malonic thioester **10** to tosyl imine **11**, catalyst **12** deprotonates the malonic acid thioester followed by a decarboxylation event to generate a stabilized thioacetate enolate. This Mannich-type addition proceeds through a stabilized enolate, then reacts with facial selectivity to the imine due to steric-tuning from **12**.



Scheme 13.3

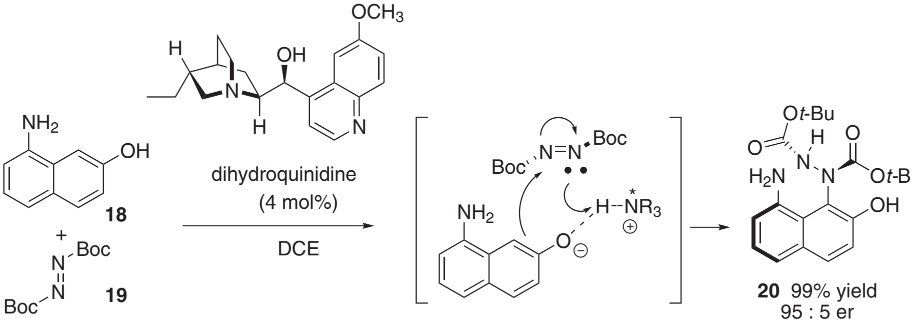
For activation of more unconventional substrates in the asymmetric addition to imines, Ricci and coworkers [13d] investigated the utility of asymmetric phosphonylation. The hydrophosphonylation of imines was achieved to provide α-amino phosphonates products in high yields and good selectivities. In a catalyst screen of various cinchona alkaloids, the role of the C(9)-hydroxyl group of the catalyst was found to be essential to drive the addition of diethyl phosphate **15** to *N*-Boc imine **14** (Scheme 13.4). It is proposed that the bifunctional role of the free hydroxyl group with the Brønsted basic quinuclidine nitrogen activation of phosphonate into a nucleophilic phosphite species was key to the reactivity. Replacing the C(9)-OH group with esters or amides erodes the selectivity of the reaction. Subsequently, quinine was the catalyst of choice.



Scheme 13.4

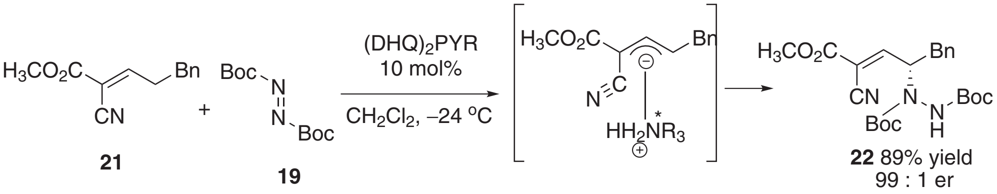
13.2.4
Asymmetric Aminations

An alternative route to asymmetric aminations utilizing azodicarboxylates as electrophiles was achieved via cinchona alkaloid activation. Through dihydroquinine (DHQ) (**17**) catalyzed asymmetric Friedel–Crafts reaction, Jørgensen *et al.* [14] reported the synthesis of N-aryl atropisomers. Methodology development for the synthesis of aryl and biaryl atropisomers used in chiral ligand development is a challenge in regards to achieving high stereoselectivity; furthermore, few reports successfully utilize substrates where a heteroatom is directly attached to the aromatic ring. Jørgensen's methodology highlights the use of a Brønsted base catalyst for selective deprotonation of the hydroxy group on 2-naphthol **19** followed by addition of a *tert*-butyl-azodicarboxylate **19** (Scheme 13.5). The corresponding aminated naphthol compound was obtained in almost quantitative yield in high enantiomeric ratios; the enantiomers are easily isolable by HPLC. The free amino and hydroxy functionality on the resulting chiral products can be easily employed in subsequent transformations towards chiral ureas in good yields without racemization.



Scheme 13.5

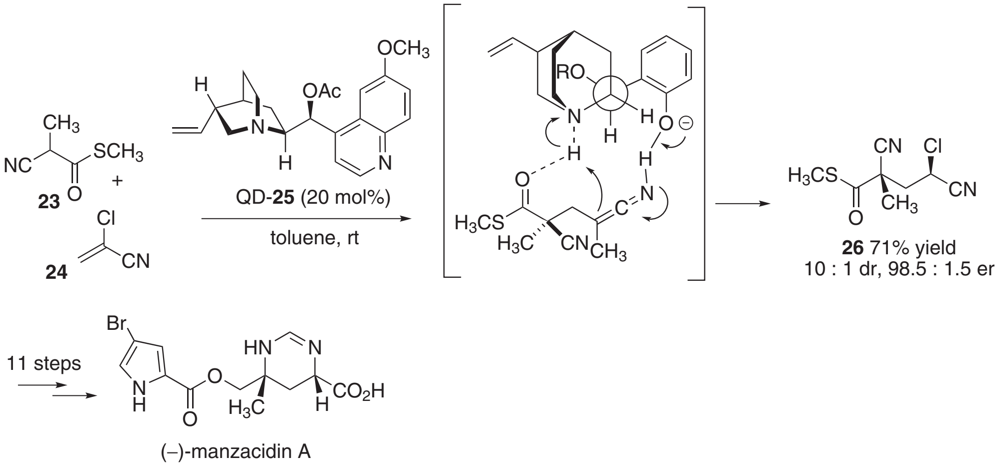
Under a different manner of cinchona alkaloid activation, azodicarboxylates were utilized as substrates for enantioselective allylic aminations. The electrophilic addition of nucleophiles to electron-withdrawing allylic C–H bonds (**21**) was feasible via activation by a chiral Brønsted base, DHQ(2PYR) (Scheme 13.6) [15]. This discovery, from Jørgensen's group, highlights the first enantioselective, metal-free allylic amination using alkylidene cyanoacetates with dialkyl azodicarboxylates.



Scheme 13.6

13.2.5
Asymmetric Activation of Isocyanoacetates

Modified cinchona alkaloids have helped highlight the versatility of the catalyst's role in asymmetric conjugate additions of α-substituted α-cyanoacetates. The utility of such transformation offers the one-step construction of chiral acyclic adducts with non-adjacent, 1,3-tertiary-quaternary stereocenters. Deng's group [16], based on their mechanistic studies, proposed a transition state that employs the quinoline C(6′)-OH and quinuclidine moiety to induce a tandem conjugate addition–protonation reaction. Under this asymmetric bifunctional catalysis, tertiary and quaternary stereocenters are generated in a stereogenic manner. The efficient stereocontrol of the chiral catalyst is demonstrated by the generation of two stereocenters from readily available achiral starting materials in a one-step tandem reaction. The utility of the chiral adducts with1,3-tertiary-quaternary stereocenters was highlighted in the subsequent 11-step synthesis towards (−)-manzacidin A (**27**) (Scheme 13.7). The first total synthesis of (−)-manzacidin A was reported by Ohfune and coworkers [17] in a 22-step synthesis.



Scheme 13.7

13.2.6
Asymmetric Diels–Alder Reaction

Most asymmetric Diels–Alder reactions undergo strong Brønsted acid catalysis, such as with binaphthol-based phosphoric acids or BINOL-based phosphoamides [18]. Dienes such as 2-pyrones are popular substrates towards the construction of bridged cyclohexene derivatives for natural product syntheses. Rather than employ Brønsted acids, early studies by Okamura and Nakatani [19] revealed that the cycloaddition of 3-hydroxy-2-pyrone with simple electron-deficient dienophiles form the *endo* adduct under base catalysis. Using simple α,β-unsaturated aldehydes as the dienophile, the Diels–Alder reaction gives moderate reactivity with a simple tertiary amine base such as NEt_3. Yet, under the activation of a chiral Brønsted base such as cinchona alkaloids, superior selectivity for the reaction is noted. More recently, the use of C9-substituted cinchona alkaloids enabled the dienophile pool to include 3-hydroxy-2-pyrone with various α,β-unsaturated ketones in the Diels–Alder reaction (Figure 13.5) [20]. The mechanistic proposal of how the catalyst works suggests that hydrogen-bonding species raise the HOMO of the 2-pyrone while lowering the LUMO of the dienophile with steric-induced stereocontrol over the activated substrates. Replacing the C(6′)-OH moiety with C(6′)-OCH_3, abolishes the reactivity of the system.

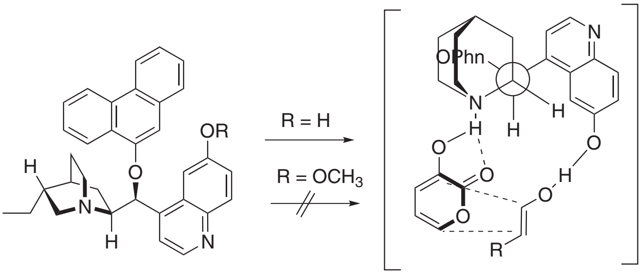


Figure 13.5 Cinchona alkaloid catalyzed cycloaddition.

13.3
Brønsted Base-Derived Thiourea Catalysts

Hydrogen-bonding moieties such as ureas and thioureas are common functional Brønsted acids extensively studied and utilized in the field of organocatalysis. The mechanistic roles of urea and thiourea catalysis were exquisitely elucidated via the works of Kelly in Diels–Alder reactions [21]. Etter's crystallographic studies [22] further clarified the hydrogen-bond interaction of thioureas. Additional work by Jørgensen and coworkers expanded the dual hydrogen-bonding activation mechanisms into Diels–Alder cycloadditions and Claisen rearrangements [23].

In light of the hydrogen-bonding abilities of thiourea catalysts, the utility of these catalysts was confined by their capability for achieving high enantioselectivities and versatility towards diverse types of reactions. Subsequently, key modifications to thioureas involved constructing groups of steric hindrance, tethering on proton-activating moieties such as Brønsted bases, and the addition of electronically polar groups to enhance the hydrogen-bonding parameters (Figure 13.6). Such a novel design for a better bifunctional catalyst has attracted the contributions of many groups, notably Jacobsen, Takemoto, Connon, Dixon, and Soós [1, 3, 24]. The most effective modifications that significantly improve catalyst performance involve tethering Brønsted bases such as cinchona alkaloids or chiral cyclohexane diamines to the thiourea. The Brønsted acidic nature of the thiourea is activated by installing aryl electron-withdrawing groups to construct a highly functionalized chiral bifunctional catalyst (Figure 13.6).

The synthetic utility of the bifunctional catalysts in various organic transformations with chiral cyclohexane-diamine derived thioureas was established through the works of Jacobsen, Takemoto, Johnston, Li, Wang, and Tsogoeva. In the last decade, asymmetric conjugate-type reactions have become popular with cinchona alkaloid derived thioureas. The next section presents non-traditional asymmetric reactions of nitroolefins, enones, imines, and cycloadditions to highlight the role of chiral Brønsted base derived thiourea catalysts.

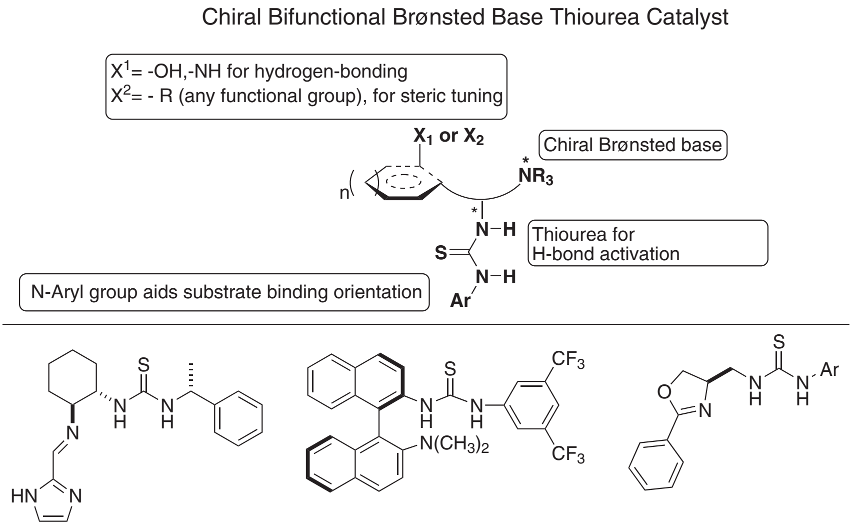
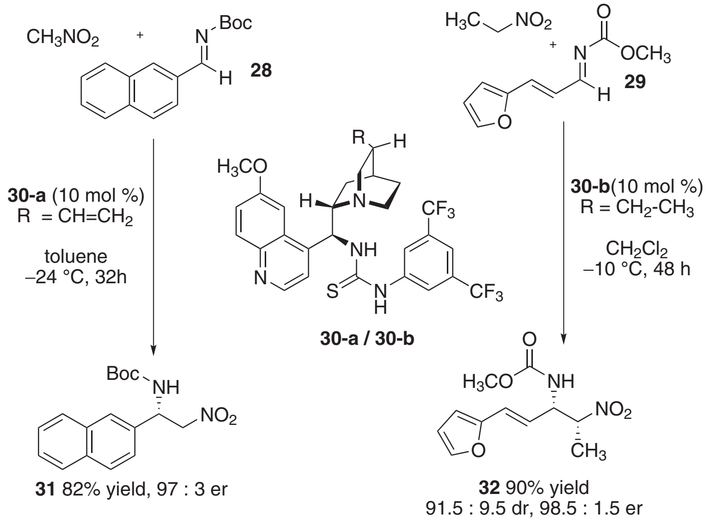

Chiral Bifunctional Brønsted Base Thiourea Catalyst
X1= -OH,-NH for hydrogen-bonding
X2= - R (any functional group), for steric tuning
X1 or X2
Chiral Brønsted base
NR3
n
N–H
S
N–H
Ar
Thiourea for H-bond activation
N-Aryl group aids substrate binding orientation
S
N H
N H
N
HN
N
S
N H
N H
CF3
CF3
N(CH3)2
S
N H
N H
Ar
O
N

Figure 13.6 Basic scaffold of chiral Brønsted base derived thiourea catalysts.

13.3.1
Asymmetric Conjugate Addition with Carbonyls and Imines

Nitroaldol (Henry) reactions of nitroalkanes and carbonyl substrates were investigated by Hiemstra *et al.* [25]. Based on their pioneering studies with cinchona alkaloid derived catalysts, moderate enantioselectivities between aromatic aldehydes and nitromethane could be achieved. From the Henry reaction, conjugate additions of nitroolefins and nitroalkanes to imines (aza-Henry) proceed well under cinchona alkaloid catalysis although the substrate pool is limited by the enantioselectivity of the reactions. Catalyst design began to focus around the cinchona alkaloid derived thioureas to more efficiently achieve highly optically active β-nitroamine products. Starting from 2005, many accounts of chiral Brønsted base derived thioureas have been published in the field of aza-Henry reactions, broadening the versatility of the reaction to various imine substrates and nitroolefins.

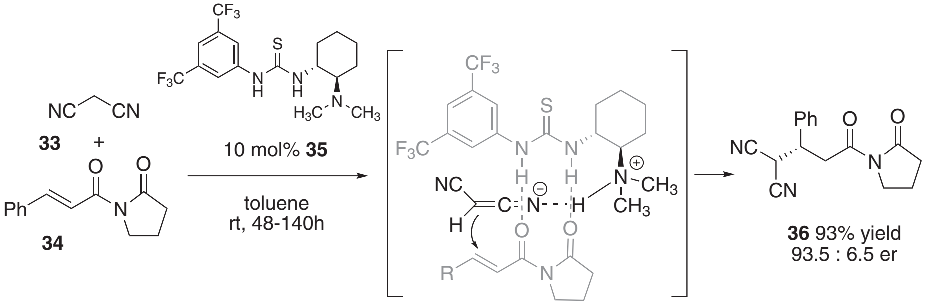
A dihydroquinidine-derived chiral thiourea (DHQD-**30**), which demonstrated significantly better stereocontrol than other cinchona alkaloids, was utilized in the aza-Henry reaction with nitroalkanes and aldimines by Schaus and coworkers (Scheme 13.8) [26]. The utility of the nitroethane pronucleophile conveniently offers a tertiary stereogenic center in the β-nitroamine product **32**. The methodology is also conveniently applicable to novel α,β-unsaturated aliphatic imines **29**, which are difficult substrates in asymmetric conjugate addition reactions. Similar reaction conditions can be applied towards to the use of dimethyl malonates as pronucleophiles that generate adducts in high enantioselectivity, which then convert smoothly into β-amino esters under the Nef conditions.



Scheme 13.8

13.3.2
Asymmetric Conjugate Additions with Non-Traditional Substrates

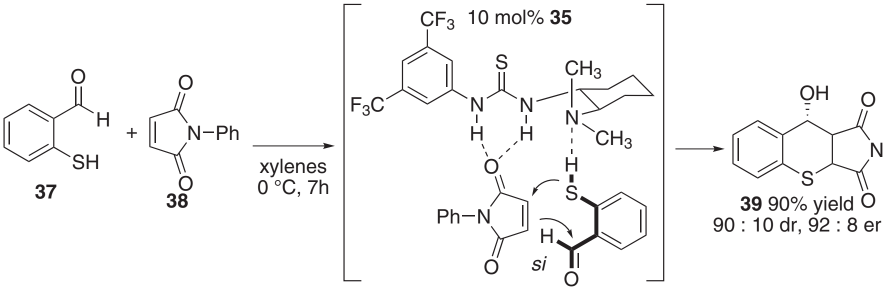
The first enantioselective organocatalytic Michael addition of malonitrile to α,β-unsaturated imides was carried out using chiral cyclohexane-diamine derived thiourea **35** (Scheme 13.9) [27]. The scope of this asymmetric Michael addition was investigated with various aliphatic and aromatic α,β-unsaturated imides. In general, excellent enantioselectivities were observed. The robust stereoselectivity of the reaction was attributed to the hydrogen-bonding interaction between the diketone of the imide and the thiourea. The electron-withdrawing trifluoromethyl groups at the 3,5-positions of the aromatic ring tethered to the thiourea were



Scheme 13.9

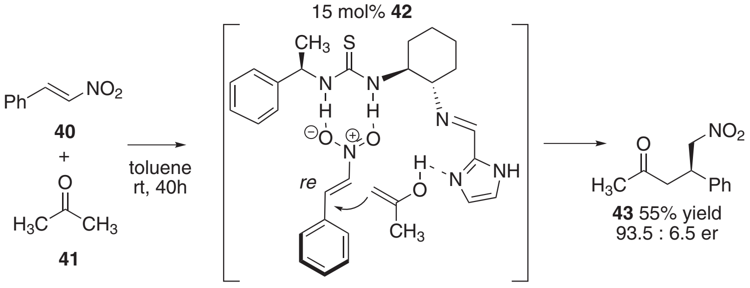
essential in strengthening the Brønsted acidity of the thiourea. The Brønsted base interaction between the tertiary amine and the malonitrile tautomer was essential in the pre-transition state for good reactivity and clean enantioselectivity.

The asymmetric conjugate addition with thiol nucleophiles was demonstrated using 2-mercaptobenzaldehydes. The utility of the same chiral cyclohexane-diamine catalysts **35** mediated the domino Michael-aldol of 2-sulfanylbenzaldehydes with maleimides (Scheme 13.10) [28]. The products of the reaction consist of fused heterocycles in high yield and high enantiomeric ratios. The stereochemical outcome sheds insight into the proposed mechanism whereby the catalyst simultaneously activates the thiol group via the cyclohexyl tertiary amine while the maleimide is stabilized by the thiourea component.



Scheme 13.10

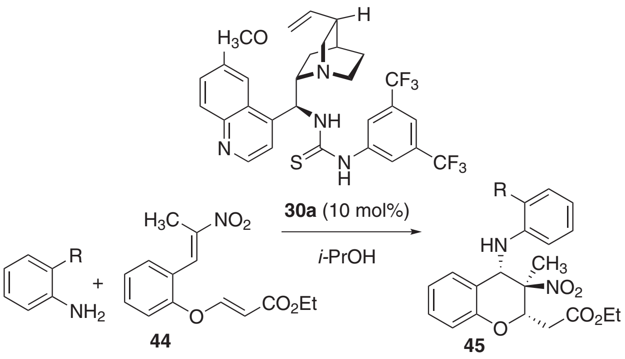
Most of the conjugate additions of enones, such as Michael additions or 1,3-dicarbonyls, typically required activation of the methylene unit of the 1,3-dicarbonyl substrate. Of note is one particular catalyst (**42**) that can activate simple carbonyls, such as acetone [29]. The chiral cyclohexane diamine-derived thiourea catalyst that includes an imidazole side-arm proved optimal in the Michael additions of acetone to β-substituted nitroolefins (Scheme 13.11). Mechanistically, the proposed role of the imidazole is to act as the Brønsted base through coordinating to the acetone tautomer, while the thiourea functionality concurrently activates the nitro group via traditional Brønsted acid interaction.



Scheme 13.11

13.3.2.1 Asymmetric Cascade Reactions

The novel scope of chiral bifunctional Brønsted base catalysts was demonstrated in work published in 2010 exploring an asymmetric aza-Michael–Michael cascade reaction of nitroolefins (Scheme 13.12) [30]. The 4-aminobenzopyran products of such a methodology are composed of three consecutive stereocenters (one of which is a quaternary stereocenter). The methodology is designed so that the thiourea portion of the catalyst (**30a**) activates the nitroolefin enolate while the tertiary amine activated the nucleophilic anilines. The initial activation step then involves an intermolecular aza-Michael reaction of nitroolefin enolates via a *Si*-face attack, followed by intramolecular Michael addition through a *Re*-face attack to form the aminobenzopyrans. The use of a polar protic solvent, isopropanol, did not disrupt hydrogen-bonding interactions of the reaction system and, surprisingly, produced the highest yields and enantioselectivities.



R = OH	R = CH_3	R =OCH_3
98% yield	88% yield	70% yield
95 : 5 dr; 98 : 2 er	95 : 5 dr; 99 : 1 er	95 : 5 dr; 96 : 4 er

Scheme 13.12

13.4
Chiral Guanidine Catalysts

The significance of the bifunctional Brønsted base catalysts is attributed to their ability to activate and stabilize both nucleophiles and electrophiles. Only a few examples of a pure Brønsted base interaction for asymmetric catalysis have appeared. Guanidines, however, have emerged as powerful superbases in organic chiral transformations (Figure 13.7) [31]. The resonance stabilization of the conjugate acid of guanidine moieties means that these catalysts are some of the strongest bases in organocatalysis.

The catalyst's unique Brønsted basic hydrogen-bonding interaction was highlighted in the asymmetric Strecker reaction in the work of Lipton in 1996 [32]. Corey's group, in 1999, designed a bicyclic C_2-symmetric chiral guanidine that has become a popular catalyst template in chiral guanidine catalysis (Figure 13.8, **46**)

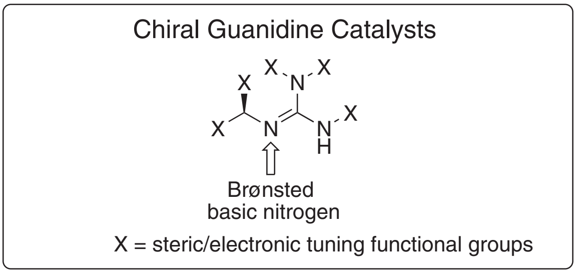

Chiral Guanidine Catalysts
X
X
X
X
X
X
N
N
N
H
Brønsted
basic nitrogen
X = steric/electronic tuning functional groups

Figure 13.7 Scaffold of chiral guanidine catalysts.

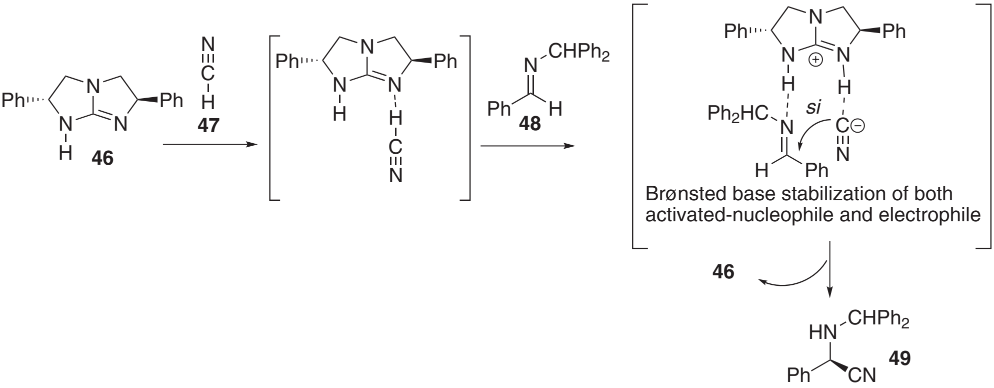

Ph
Ph
N
N
N
H
46
N
C
H
47
H
C
N
N
CHPh2
Ph
H
48
Ph2HC
si
C⊖
N
⊕
Brønsted base stabilization of both activated-nucleophile and electrophile
46
HN
CHPh2
Ph
CN
49

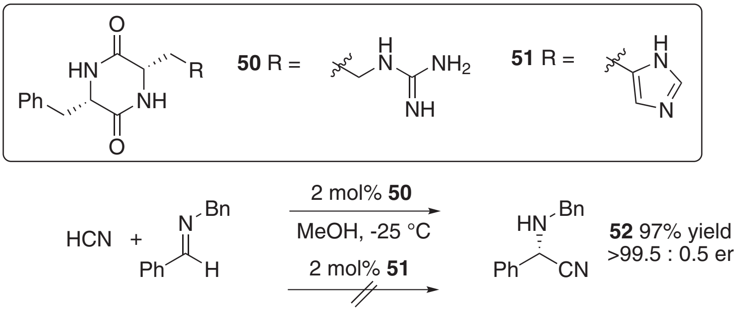
Figure 13.8 Proposed catalytic cycle for chiral guanidine promoted hydrocyanation.

[33]. The proposed mechanism presents the nucleophile undergoing a formal Brønsted base interaction with the guanidine catalyst, thus activating the hydrocyanate for addition to the stabilized electrophile. In comparison to bifunctional catalysts, the guanidines are basic enough to activate and stabilize both nucleophile and electrophile without assistance from other types of hydrogen-bond interactions.

13.4.1
Asymmetric Conjugate Addition to Enones and Imines

In 1994 Chinchilla and coworkers [34] identified and synthesized a chiral guanidine for the asymmetric catalytic addition of nitroolefins to aldehydes. Since this initial discovery, numerous developments in the field of asymmetric Brønsted base catalysis have utilized chiral guanidines.

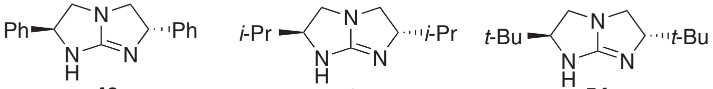
Lipton and coworkers [32] reported the use of a cyclic dipeptide guanidine catalyst for the asymmetric Strecker reaction. In a comparison between an imidazole moiety and a guanidine moiety for the Brønsted basic unit of the catalyst, a large discrepancy in the reactivity became evident. The highly basic guanidine functional group of catalyst **50** drove the reaction to high yields, even at low temperatures, with excellent enantioselectivities (Scheme 13.13). The imidazole moiety of **51** was simply not basic enough to achieve the desired reactivity.



Scheme 13.13

Corey's C_2-symmetric bicyclic guanidine catalyst scaffold subsequently initiated further investigation of related guanidine scaffolds for the asymmetric addition of nitroalkanes to α,β-unsaturated ketones (Figure 13.9). Tan and coworkers [35] using similar bicyclic guanidine catalysts reported Michael adducts in decent yields and moderate selectivities. Their scope of substrates also expanded to malonates as pronucleophiles, providing γ-nitro adducts in high yields, albeit with compromised selectivities. The degradation in stereoselectivity of the reaction was attributed to weaker interactions between the guanidine and malonate pronucleophiles, as compared to nitroalkanes, which form tighter bound ion pairs in nonpolar solvents. The asymmetric induction via chiral bicyclic guanidines appears to be significantly more efficient for highly charged pronucleophiles, such as nitroalkanes and nitroolefins, for the tighter coordination necessary in asymmetric conjugate addition reactions.

Another structurally modified guanidine, catalyst **57**, was reported by Ishikawa *et al.* [36] for asymmetric Michael additions of glycine imines to acrylates under neat conditions. The high conversion and selectivity was attributed to the relative configuration of the three chiral centers of the catalyst in the absence of any solvent interactions. A reversal of stereochemistry may be achieved when the chiral center



46 **53** **54**

Corey's chiral bicycllic guanidine

Figure 13.9 Some bicyclic guanidine catalyst scaffolds.

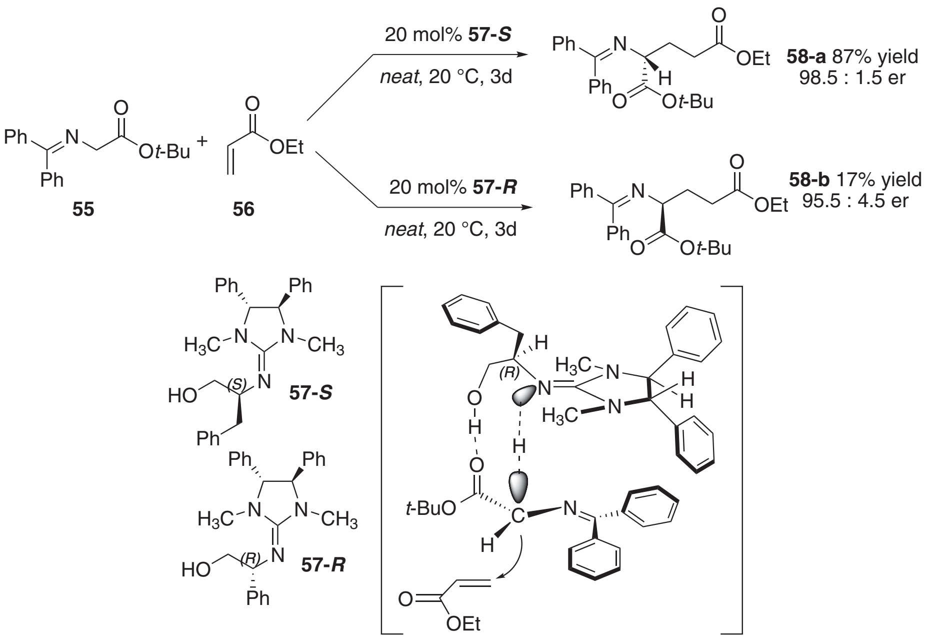
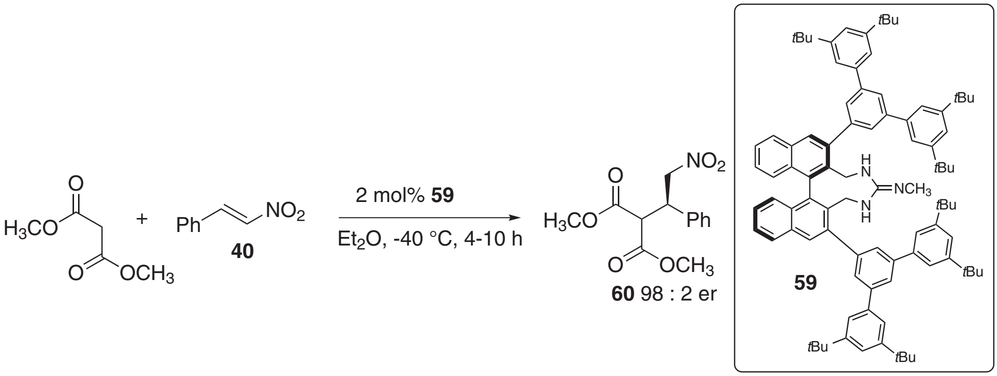


Figure 13.10 Proposed pre-transition state for the Michael addition of glycines.

adjacent to the imino nitrogen is switched from (*S*) to (*R*). The proposed pre-transition state illustrates the blockage of the *Re*-face of the nucleophile by the (*R*)- guanidine catalyst (Figure 13.10).

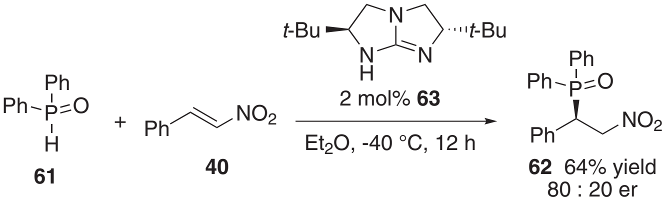
A sterically-congested novel guanidine catalyst with a chiral 3 for the asymmetric addition of dicarbonyl compounds to nitroolefins was developed by Terada and coworkers (Scheme 13.14) [37]. Sterically-congested substitutions



Scheme 13.14

on the binaphthol backbone **59** dramatically increased enantioselectivity; 3,5-substitions on the aromatic rings with di-*tert*-butylphenyl groups on the 3,3′-position of the binaphthol backbone provided reproducible high yields and selectivities. Catalyst **59** enabled the scope of the reaction to include a larger pool of highly activated pronucleophiles such as aliphatic or aromatic nitroalkenes and α-substituted β-ketoesters, while maintaining overall good yields and enantioselectivity.

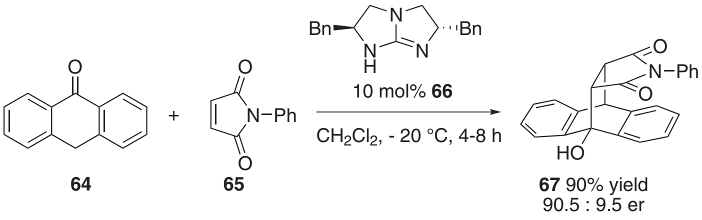
A current addition to novel asymmetric bond formation besides carbon–heteroatom and carbon–carbon bonds is new bond formation involving phosphorous and carbon atoms. In nature, enantioselective carbon–phosphorous bond formation is driven by *in vivo* enzymes, such as the phosphonylation and phosphoamidation (subsequent *in vivo* activation) of many antiviral compounds [38]. Few organocatalytic phospha-Michael reactions have been reported, but Tan and coworkers [39] have presented the asymmetric addition of phosphine oxides to nitroolefins (Scheme 13.15). Chiral nitro-amino phosphines in high yield and high enantiomeric ratios were achieved through the use of chiral bicyclic guanidine **63** using only a 2 mol% catalytic loading. The catalyst was applicable to both electron-withdrawing and electron-donating β-aryl-nitroolefins without erosion of yields and stereoselectivities for the reaction.



Scheme 13.15

13.4.2
Asymmetric Diels–Alder Reactions

The first organocatalytic enantioselective guanidine catalyzed Diels–Alder reaction was disclosed in 2006 [40]. Although Brønsted base catalyzed Diels–Alder reactions have been reported for cinchona alkaloid catalysts, the vast majority of such cycloadditions are catalyzed by Lewis acids or chiral secondary amines. Using a derivative of Corey's C_2-symmetric bicyclic guanidine catalyst, Tan and coworkers [39] demonstrated the utility of a pure Brønsted base catalyst in promoting the Diels–Alder reaction between anthrones and N-substituted maleimides in good yields and high enantioselectivities (Scheme 13.16).



Scheme 13.16

13.5
Conclusion

The utility and function of chiral Brønsted bases clearly demonstrate their indispensable role in organocatalysis. The versatility in the reaction scope of cinchona alkaloids, chiral Brønsted base derived thioureas, and chiral guanidines strongly establishes the significance of hydrogen-bonding interactions in asymmetric synthesis. Moreover, it is the fine-tuning of such interactions via Brønsted basic moieties acting alone or complementarily with Brønsted acidic functional groups that confer the necessary parameters to achieve optimal results.

The search for new catalyst functions is partly inspired by the design of natural molecules such as the cinchona alkaloids, and partly motivated by the novelty of synthetic molecules such as the chiral guanidines. In addition to the high levels of stereoinduction attainable through synergistic interactions of hydrogen-bond donors or activators, chiral Brønsted base organocatalysis has included a notable range of reactive substrates while maintaining low catalyst loadings.

The focus of organocatalytic Brønsted bases will continue to evolve towards catalysts that can more efficiently activate reaction systems that may seem feasible in theory yet, in practice, encounter energy barriers that prevent the desired yields and selectivity. Our evolving knowledge of the asymmetric organocatalytic field, complemented by computational resources, can offer new avenues of exploration towards rational design of new scaffolds.

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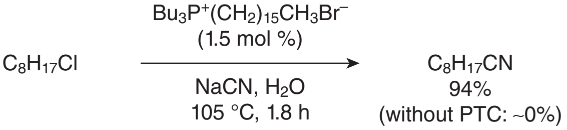
14
Chiral Onium Salts (Phase-Transfer Reactions)

Seiji Shirakawa and Keiji Maruoka

14.1
Introduction

In 1971, Starks introduced the term "phase-transfer catalysis" to explain the critical role of tetraalkylammonium or phosphonium salts (Q^+X^-) in the reactions between two substances located in different immiscible phases [1]. For example, the displacement reaction of 1-chlorooctane with aqueous sodium cyanide is accelerated many thousandfold by the addition of hexadecyl(tributyl)phosphonium bromide as a phase-transfer catalyst (Scheme 14.1). Key to this tremendous enhancement in reactivity is the generation of quaternary phosphonium cyanide, which makes the cyanide anion soluble in organic solvents and sufficiently nucleophilic. The high rate of displacement is mainly due to the two characteristic features of the pairing cation (Q^+): high lipophilicity and the large ionic radius.



$$C_8H_{17}Cl \xrightarrow[\text{NaCN, } H_2O,\ 105\ ^\circ\text{C, 1.8 h}]{Bu_3P^+(CH_2)_{15}CH_3Br^-\ (1.5\ \text{mol \%})} C_8H_{17}CN\ \ 94\%\ (\text{without PTC: } \sim 0\%)$$

Scheme 14.1

Although it was not the first observation of the catalytic activity of quaternary onium salts, the foundations of phase-transfer catalysis were laid by Starks together with Makosza and Brändström in the mid- to late-1960s [2]. Since then, the chemical community has witnessed an exponential growth of phase-transfer catalysis as a practical methodology for organic synthesis. The advantages of this method are its simple experimental procedures, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations [3]. Nowadays, it appears to be the most important synthetic method used in various fields of organic chemistry, and has also found widespread industrial applications.

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In contrast, the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, non-racemic catalysts has progressed rather slowly, despite its potential to create a new area of asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetraalkylonium ions (Q^+). However, recent efforts in this direction have resulted in notable achievements, thus making it feasible to perform various bond-formation reactions under the mild conditions used in phase-transfer catalysis [4].

Based on the design of chiral quaternary onium bromides and chlorides as chiral phase-transfer catalysts, chiral quaternary onium fluorides [5] and phenoxides [6] have been developed as chiral base catalysts for homogeneous reactions.

This chapter aims to assist the reader to generate an intuitive understanding of the catalyst types, reaction classes, and mechanism of chiral onium salts catalyzed asymmetric reactions.

14.2
Phase-Transfer Catalysis

14.2.1
Phase-Transfer Reaction of Active Methylene or Methine Compounds with Inorganic Base

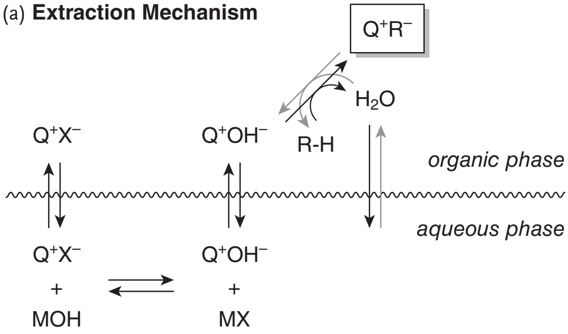
The representative reaction system applied in asymmetric phase-transfer catalysis is the biphasic system composed of an organic phase containing an active methylene or methine compound and an electrophile, and an aqueous or solid phase of inorganic base such as alkali metal (Na, K, Cs) hydroxide or carbonate. The key reactive intermediate in this type of reaction is the onium carbanion species, mostly onium enolate or nitronate, which react with the electrophile in the organic phase to afford the product.

14.2.1.1 Generation of Onium Carbanion

The exact pathway for generating the reactive onium carbanion species remains the subject of controversy, typically between Starks extraction mechanism (Figure 14.1a) and the Makosza interfacial mechanism (Figure 14.1b). In the Starks extraction mechanism, the phase-transfer catalyst moves back and forth across the organic and aqueous phases. The onium salt equilibrates with the inorganic base in the aqueous phase, and extracts hydroxide into the organic phase. The onium hydroxide then abstracts hydrogen from the acidic organic compound to give the reactive intermediate Q^+R^- (Figure 14.1a).

The advocated pathway of the interfacial mechanism is the prior formation of metal carbanion at the interface of organic and aqueous phase in the absence of phase-transfer catalyst, followed by extraction of the formed metal carbanion species from the interface into the organic phase by the action of phase-transfer catalyst (Figure 14.1b).

(a) **Extraction Mechanism**



(b) **Interfacial Mechanism**

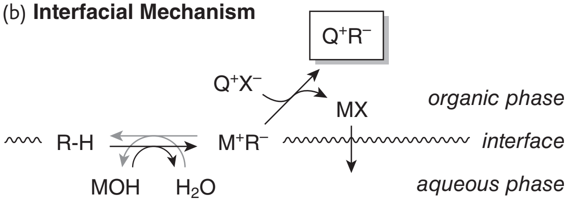


Figure 14.1 Pathways for generating the reactive onium carbanion species.

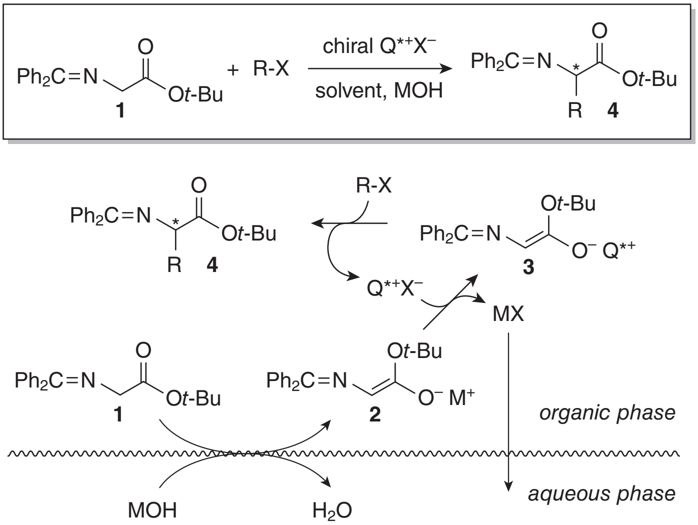
Since asymmetric phase-transfer catalysts normally contain highly lipophilic chiral organic frameworks, and are reluctant to enter the aqueous phase, the Makosza interfacial mechanism seems plausible.

Clearly, the area of the interface and the basicity of the inorganic salt affect the amount of available onium carbanion. Notably, an excessively lipophilic phase-transfer catalyst would hardly access the interface, and consequently the use of such a catalyst would result in an insufficient reaction.

14.2.1.2 **Nucleophilic Substitution**

The fate of the onium carbanion Q^+R^- incorporated into the organic phase depends on the electrophilic reaction partner. The most studied area in the asymmetric phase-transfer catalysis is that of asymmetric alkylation of active methylene or methine compounds with alkyl halides, in an irreversible manner. The reaction mechanism illustrated above is exemplified by the asymmetric alkylation of glycine Schiff base (Scheme 14.2) [7].

In the first step, glycine Schiff base **1** reacts with the inorganic base at the interface of two phases to give the metal enolate **2,** which remains at the interface due to its highly polar character. The metal enolate **2** then exchanges the cation to provide onium enolate **3**. The sufficiently lipophilic **3** then moves into the organic phase to react with alkyl halide. After the reaction, onium halide ($Q^{*+}X^-$) is regenerated and enters the next catalytic cycle. The key issue to be considered here is the possibility of product racemization and dialkylation. In this example, the basicity



Scheme 14.2

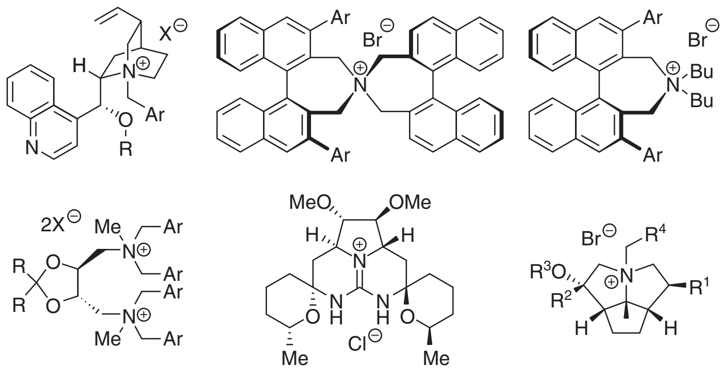
of the inorganic base and the acidity of the substrate and product, as well as other reaction conditions, are carefully adjusted to circumvent this problem. Notably, control of the E/Z geometry of the enolate is apparently critical to the asymmetric induction, although there is no clear evidence about which isomer is the actual reacting species in this case.

Representative chiral phase-transfer catalysts ($Q^{*+}X^{-}$) for the asymmetric alkylation of glycine Schiff base **1** are summarized in Figure 14.2a [8–13]. These catalysts were also applied to other asymmetric alkylations with different nucleophiles (Figure 14.2b) [14–17].

14.2.1.3 **Nucleophilic Addition**

Unlike nucleophilic substitution reactions, which generate stable onium halide after the reaction, nucleophilic additions to electrophilic C=X double bonds (X = C, N, O) provide rather basic onium anion species as an initial product. If the anion is sufficiently stable under the reaction conditions, the onium anion will then exchange the counter ion for the other metal carbanion at the interface to regenerate the reactive onium carbanion $Q^{+}R^{-}$. In another scenario, the basic onium anion may abstract the acidic hydrogen atom of the other substrate to provide $Q^{+}R^{-}$ directly. Such a reaction system ideally requires only a catalytic amount of the base although, in general, a substoichiometric or excess amount of the base is used to lead the reaction to completion. An additional feature of this system is the substantial possibility of a retro-process at the crucial asymmetric induction step, which might be problematic in some cases.

The direct asymmetric aldol reaction under phase-transfer conditions is a representative example of this class of phase-transfer reaction, which is known to proceed with a catalytic amount of base and to include an undesired retro-process (Scheme 14.3) [18]. Here, the onium enolate **3** reacts with aldehyde in the organic


(a) **Chiral Phase-Transfer Catalysts**

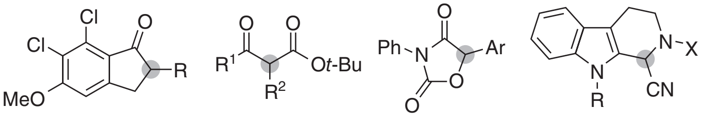
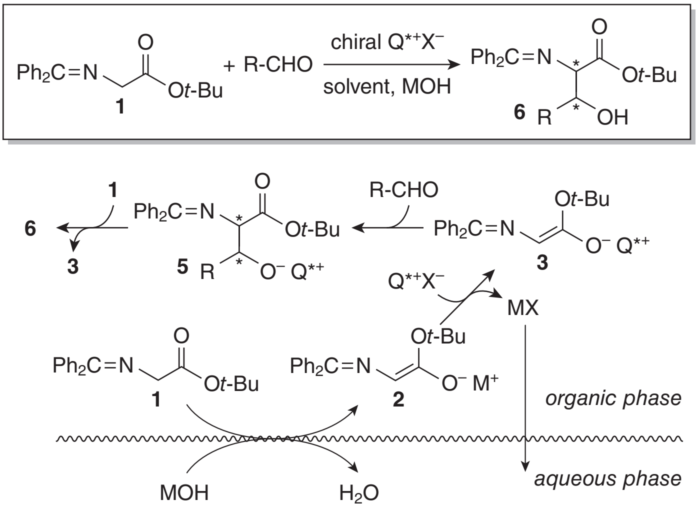

(b) **Substrates for Asymmetric Alkylation**

Figure 14.2 (a) Chiral phase-transfer catalysts ($Q^{*+}X^{-}$) for the asymmetric alkylation of glycine Schiff base **1**; (b) substrates for asymmetric alkylations.

phase to give the onium alkoxide **5**, which may abstract the hydrogen from the other glycine Schiff base **1** to provide another reactive intermediate onium enolate **3** and the protonated aldol product **6**. Notably, this is not the only expected pathway, and there are complex equilibria in this reaction system, which, for reasons of clarity, are not fully delineated below.



Scheme 14.3

The phase-transfer-catalyzed asymmetric conjugate additions [19] and Mannich reactions [20] are other typical examples that fall into this category.

14.2.2
Phase-Transfer Catalyzed Addition of Anion Supplied as Metal Salt

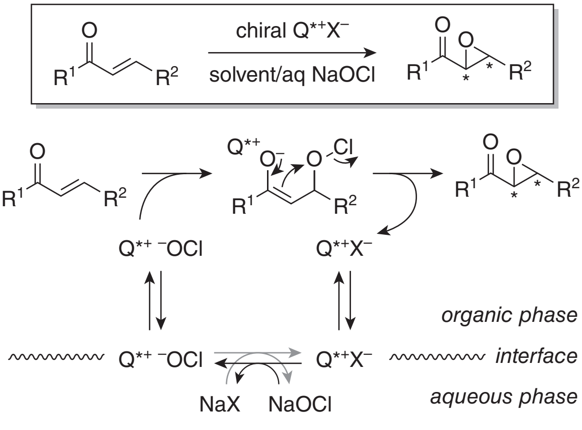
The common feature in the asymmetric phase-transfer catalysis introduced above is the formation of the reactive onium carbanion from the inorganic base and active methylene or methine compounds, followed by extraction of the carbanion species as the onium salt from the interfacial area into the organic phase. Thus, both reagents normally remain in the organic phase. In the other category of asymmetric phase-transfer catalysis, the anion itself supplied as an aqueous solution or solid of its inorganic salt as the reaction partner and the two reactants are strictly separated by the interface. In such a system, the anion is transferred gradually from the aqueous phase into the organic phase by the intervention of an onium salt.

With regards to the mechanism of the generation of onium anion, the Starks extraction mechanism and interfacial mechanism (Brändström–Montanari modification) are suggested [1–3]. As in the above-described case, the interfacial mechanism seems to be operative in the asymmetric phase-transfer catalysis.

The reaction conditions are rather mild, so that the possibility of side reactions, such as catalyst decomposition, is considerably reduced. The major challenge associated with these reactions is an absence of prochirality in the anionic species. Namely, the chiral onium anion must discriminate the enantiotopic face of the distant electronically neutral reaction partner in the organic phase.

Asymmetric phase-transfer catalyzed oxidation of olefin using sodium hypochlorite or potassium permanganate as metal anion sources is the typical example of this category.

The asymmetric epoxidation of an α,β-unsaturated ketone, using sodium hypochlorite, is illustrated in Scheme 14.4 [21]. Hypochlorite is extracted as an



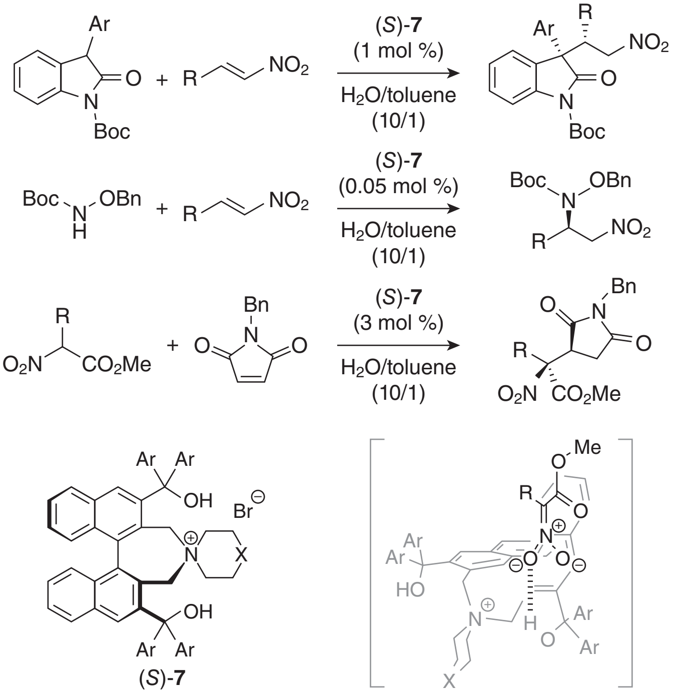
Scheme 14.4

onium salt into the organic phase, and the onium hypochlorite then reacts with the ketone while recognizing its enantiotopic face to provide the optically enriched α,β-epoxy ketone.

Phase-transfer-catalyzed asymmetric cyanations [22] with potassium cyanide are also typical examples that fall into this category.

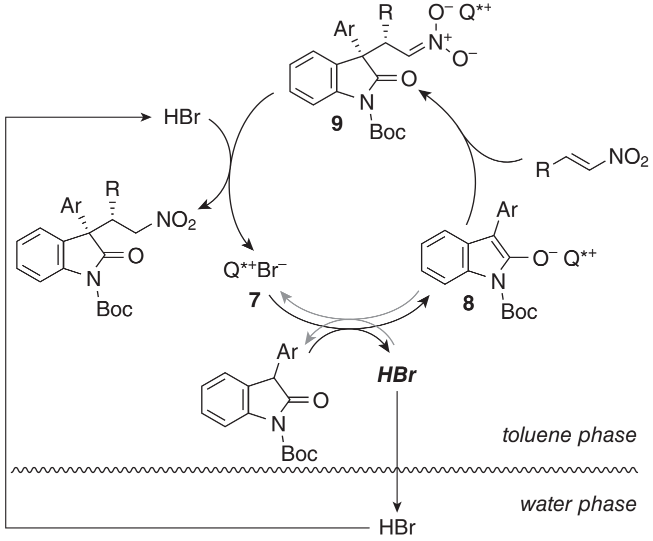
14.2.3
Base-Free Neutral Phase-Transfer Reaction

Although quaternary onium bromides and chlorides as phase-transfer catalysts are generally believed to require base additives for phase-transfer reactions of active methylene and methine compounds, which were discussed above, we have recently discovered an hitherto unknown base-free neutral phase-transfer reaction system in asymmetric conjugate additions (Scheme 14.5) [23]. The reactions were efficiently promoted by chiral bifunctional ammonium bromide (*S*)-**7** under neutral conditions with water-rich biphasic solvent. The role of hydroxy groups in the bifunctional catalyst was clearly shown in the transition-state model of the reaction based on the single-crystal X-ray structure of ammonium amide [23b] and nitronate [23c].



Scheme 14.5

Based on the characteristic features of this neutral phase-transfer reaction, an assumed catalytic cycle of the conjugate addition of 3-aryloxindole was proposed as shown in Scheme 14.6. For the promotion of the reaction, the combination of the H_2O/toluene biphasic reaction system with a lipophilic phase-transfer catalyst such as (*S*)-**7** was indispensable. In the formation of ammonium enolate **8**, HBr is simultaneously generated, and in the case of toluene solvent alone the reaction mixture becomes homogeneous and hence the reverse reaction from **8** to **7** (i.e., protonation of **8**) may be fast. However, in the H_2O/toluene biphasic reaction system, hydrophilic HBr moves into the water phase smoothly, while lipophilic ammonium enolate **8** remains in the toluene phase. Consequently, protonation by the contact of ammonium enolate **8** and HBr was suppressed, and hence the transformation from **7** to **8** was efficiently promoted. Then, ammonium enolate **8** and nitroolefin would combine in the toluene phase to promote the conjugate addition step (**8** to **9** in Scheme 14.6) smoothly.

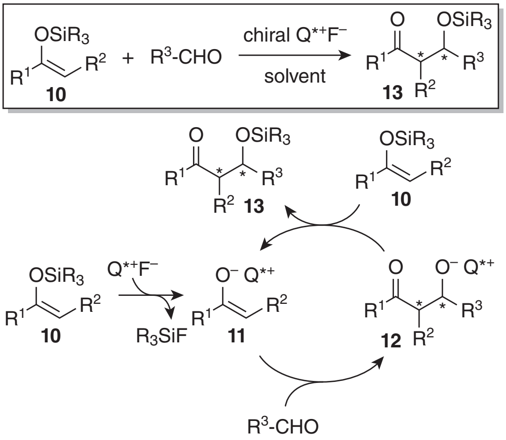


Scheme 14.6

14.3
Onium Fluorides

Quaternary onium fluorides, particularly tetraalkylammonium fluorides, have been widely recognized as a convenient, organic-soluble source of naked fluoride ion. Their utility in modern organic synthesis, taking advantage of the nucleophilic affinity of fluoride ion for a silicon atom in aprotic solvents, has been well documented on numerous occasions [24]. This property enables the fluoride-mediated generation of nucleophiles from organosilicon compounds, which have been utilized for subsequent selective bond-forming reactions under mild conditions. These synthetically useful metal-free methods have implications for the development of asymmetric versions based on the use of chiral, non-racemic quaternary ammonium fluorides, giving a unique platform for establishing otherwise difficult asymmetric transformations.

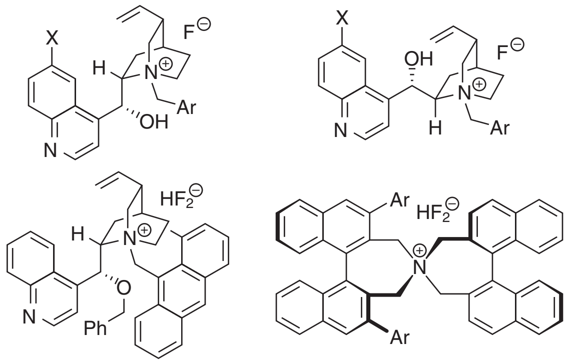
The asymmetric Mukaiyama-type aldol reaction is a representative example of ammonium fluoride-catalyzed reactions (Scheme 14.7) [25]. In the first step, silyl enol ether **10** reacts with ammonium fluoride to produce ammonium enolate **11** with generation of trialkylsilyl fluoride. The ammonium enolate **11** then reacts with aldehyde to produce ammonium alkoxide **12**. Attack of this alkoxide anion on silyl enol ether **10** leads to the regeneration of ammonium enolate **11** and the formation of silylated aldol product **13**.



Scheme 14.7

Figure 14.3a summarizes representative chiral ammonium fluoride and bifluoride catalysts. These catalysts have been applied to various asymmetric transformations with different silyl nucleophiles (Figure 14.3b) [26–29].

(a) **Chiral Ammonium Fluorides**



(b) **Silyl Nucleophiles**

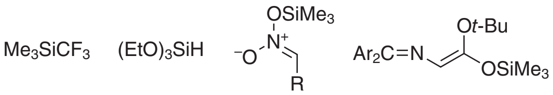


Figure 14.3 (a) Representative chiral ammonium fluoride and bifluoride catalysts; (b) silyl nucleophiles.

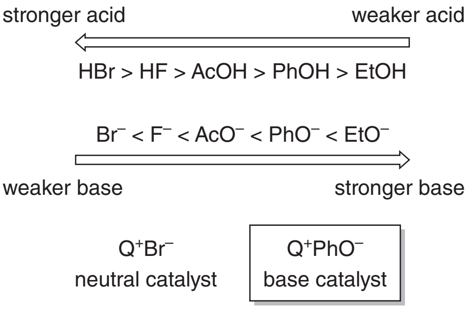


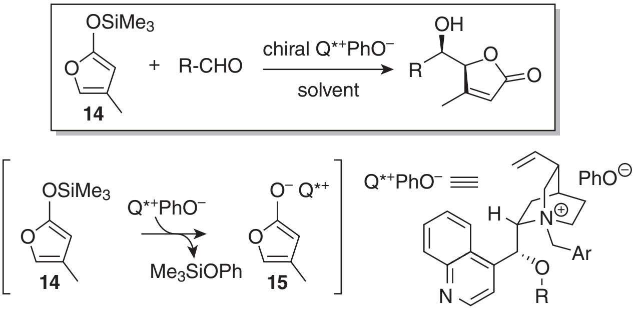
Figure 14.4 A scale of basicity.

14.4
Onium Phenoxides and Related Compounds

In contrast to the neutral property of onium bromides, onium phenoxides and carboxylates work as base catalysts by considering the general basicity of the phenoxide and carboxylate anions (Figure 14.4). Based on this property, chiral onium phenoxides and related compounds have been employed both as Lewis and Brønsted base catalysts for homogeneous reactions [6].

14.4.1
Onium Phenoxides as Lewis Base Catalysts

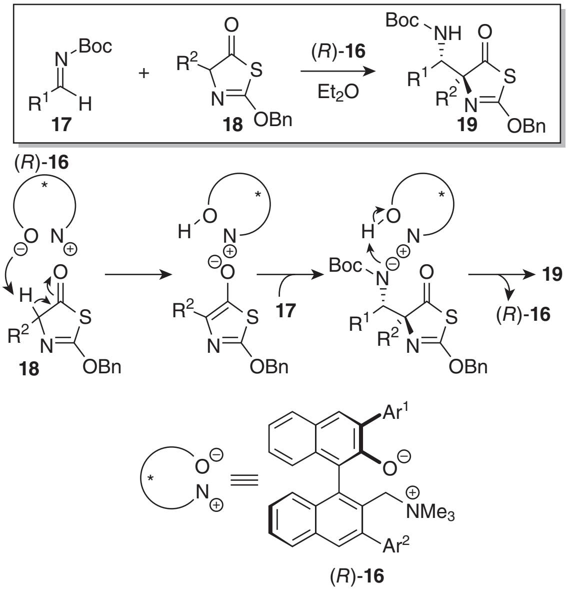
Cinchona alkaloid-derived ammonium phenoxides as Lewis base catalysts have been applied to asymmetric vinylogous Mukaiyama-type aldol reactions (Scheme 14.8) [30]. In the first step of this reaction, silyl compound **14** reacts with ammonium phenoxide to produce ammonium dienolate **15** with generation of trimethyl(phenoxy)silane. The latter part of this reaction mechanism is basically similar to the reaction mechanism of ammonium fluoride-catalyzed reactions with silyl nucleophiles as shown in Scheme 14.7. This reaction system was also applied to other asymmetric transformations [6a, 31].



Scheme 14.8

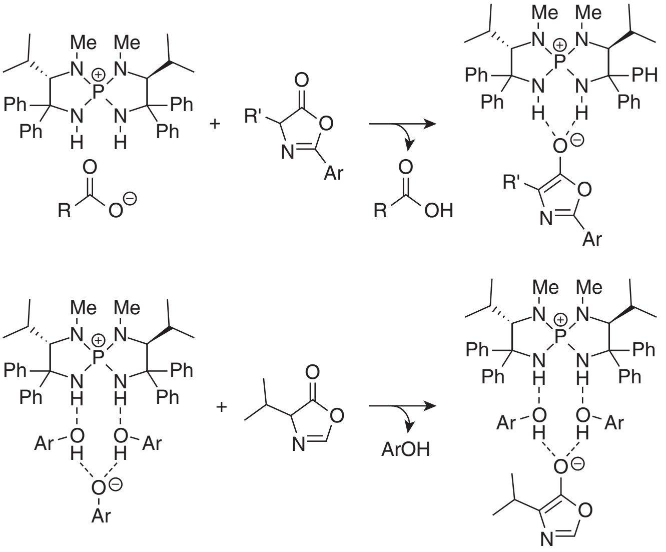
14.4.2
Onium Phenoxides and Related Compounds as Brønsted Base Catalysts

An ammonium betaine of type (*R*)-**16** could be considered as an intramolecular version of ammonium phenoxide. The potential of chiral ammonium betaine (*R*)-**16** as Brønsted base catalyst has been demonstrated in asymmetric Mannich reactions (Scheme 14.9) [6b, 32]. The basic phenoxide anion is responsible for abstraction of the active methine proton of a nucleophile **18** and thus gives the corresponding chiral ammonium enolate. Subsequent stereoselective bond formation with imine **17** afforded ammonium amide that can be rapidly protonated by the *in situ* formed phenolic hydrogen to regenerate the ammonium betaine (*R*)-**16**.



Scheme 14.9

Tetraaminophosphonium carboxylates and phenoxides have also been developed as chiral Brønsted base catalysts for asymmetric Mannich reactions and conjugate additions [6c, 33]. These catalysts recognized and activated the nucleophiles through the hydrogen-bonding network (Scheme 14.10).



Scheme 14.10

14.5
Conclusions

As described in this chapter, numerous recent efforts to elaborate chiral onium salts have greatly expanded their use as asymmetric catalysts in organic synthesis. However, the full potential of chiral onium salts is yet to be realized in terms of general applicability. Continuous efforts should be made toward the design and development of conceptually new catalysts, and to understanding the relationship between catalyst structure and stereocontrolling ability.

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15

Lewis Bases

Pavel Kočovský and Andrei V. Malkov

15.1

Introduction

Nucleophilic addition to carbonyl compounds is the cornerstone of organic synthesis, highlighted by the classical examples of Grignard reactions, aldol condensation, $LiAlH_4$ reductions, and so on. However, when less reactive nucleophiles are employed, such as allylsilane [1], allylstannane [1, 2], or Cl_3SiR [3], activation is required. Here, we have a choice of activating either the electrophile or the nucleophile. Activation of the electrophile, that is, the carbonyl reactant, can be attained by coordination of a Lewis acid to the oxygen [4], which increases the electrophilicity of the carbonyl carbon and, consequently, the reactivity of the C=O group. Alternatively, coordination of a Lewis base to the nucleophile can be assumed to increase its nucleophilicity, which should also allow the addition to occur [5]. Since only the coordinated species will react, the activator can be used in just a catalytic amount, provided that it can be regenerated after completion of the reaction and returned to the next catalytic cycle. Naturally, if the catalyst is chiral, preferential formation of one enantiomer of the product can be expected.

Of the numerous examples of asymmetric reactions catalyzed by Lewis bases, this chapter is focused mainly on the activation of silicon reagents and related processes. Various other types of Lewis basic (nucleophilic) activation, namely, the Morita–Baylis–Hillman reaction, acyl transfer, nucleophilic carbenes, and carbonyl reduction, are dealt with in other chapters.

This chapter covers the work published until the end of 2011 but selected examples of the early 2012 literature are also included. The schemes and tables were chosen to illustrate mainly the catalytic asymmetric reactions. Stoichiometric or non-asymmetric examples, relevant to the main focus, are briefly mentioned in the text, especially when further development is expected but, in general, are not presented in a graphical form. The key catalytic reactions exhibiting high enantioselectivity and the most successful catalysts are highlighted by frames. We believe that this layout will benefit the reader who wishes to obtain initial information quickly by browsing through the pages.

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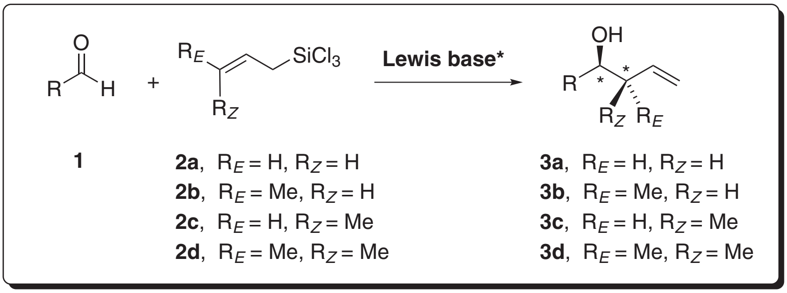
15.2
Allylation Reactions

15.2.1
Catalytic Allylation of Aldehydes

Lewis acids are known to catalyze the allylation of aldehydes **1** with AllylSiMe$_3$ and its congeners by coordination to the carbonyl group [1, 6]. By contrast, Lewis bases are typically inert to AllylSiMe$_3$ and require AllylSiCl$_3$ (**2a**) [7], whose silicon atom is more Lewis acidic (Scheme 15.1) [6–13].

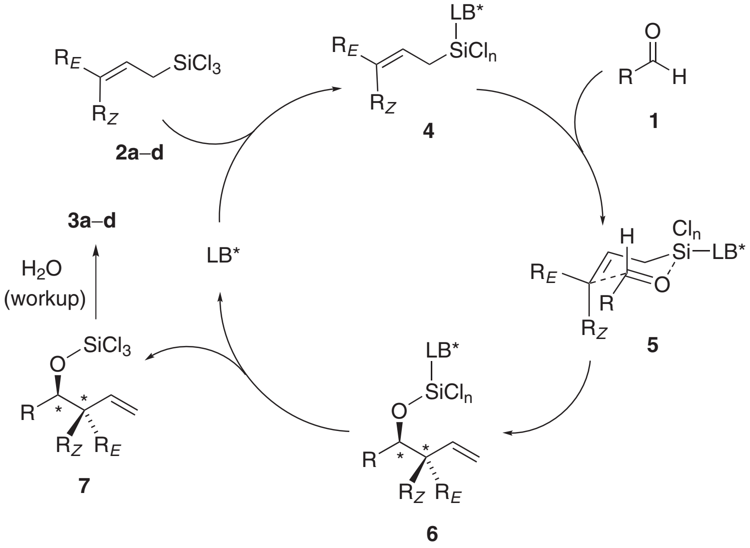

O
R
H
+
R$_E$
SiCl$_3$
R$_Z$
Lewis base*
OH
R
*
*
R$_Z$ R$_E$
1
2a, R$_E$ = H, R$_Z$ = H
2b, R$_E$ = Me, R$_Z$ = H
2c, R$_E$ = H, R$_Z$ = Me
2d, R$_E$ = Me, R$_Z$ = Me
3a, R$_E$ = H, R$_Z$ = H
3b, R$_E$ = Me, R$_Z$ = H
3c, R$_E$ = H, R$_Z$ = Me
3d, R$_E$ = Me, R$_Z$ = Me

Scheme 15.1

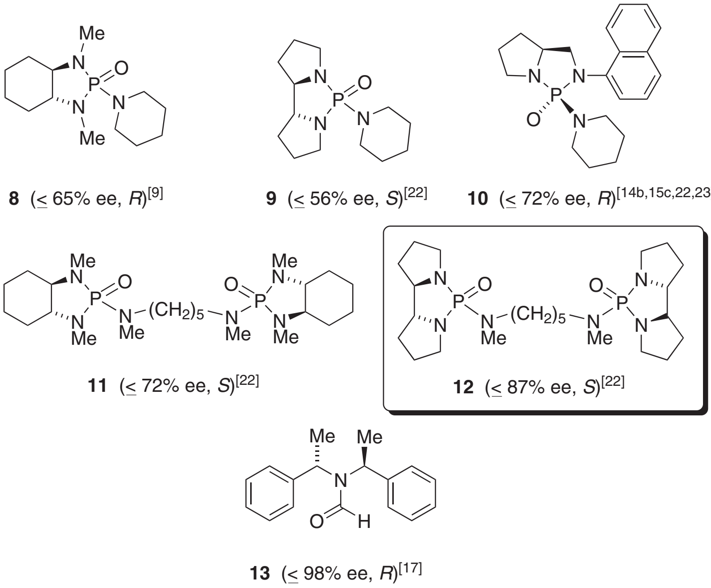
If the latter reaction proceeds through a closed transition state (e.g., **5** in Scheme 15.2), good diastereocontrol can be expected in the case of *trans*- and *cis*-CrotylSiCl$_3$ (**2b**/**2c**) [14, 15]: Here, the *anti*-diastereoisomer **3b** should be obtained from *trans*-crotyl derivative **2b**, whereas the *syn*-isomer **3c** should result from the reaction of the *cis*-isomer **2c** (Scheme 15.2). Furthermore, this mechanism creates an opportunity for transferring the chiral information if the Lewis base employed is chiral. Provided the Lewis base dissociates from the silicon in the intermediate **6** at a sufficient rate, it can act as a catalyst (rather than a stoichiometric reagent). Typical Lewis bases that promote the allylation reaction are the common dipolar aprotic solvents, such as DMF [8, 12], DMSO [8, 9], and HMPA [9, 16], and other substances possessing a strongly Lewis basic oxygen, such as various formamides [17] (in a solution or on a solid support [7, 8, 18]), urea derivatives [19], and catecholates [10] (and their chiral modifications [5c]). Note that upon coordination to a Lewis base, the silicon atom becomes more Lewis acidic (see below), which facilitates its coordination to the carbonyl in the cyclic transition state **5**.

Fluoride ion (from CsF, CdF$_2$, or AgF) can also catalyze the allylation using AllylSiF$_3$ and AllylSi(OMe)$_3$, respectively [10, 11]; the asymmetric version (with ≤56% ee) requires a combination of Bu$_4$N$^+$[SiPh$_3$F$_2$]$^-$ with the Lewis acidic complex of CuCl and BINAP [21]. While aldehydes react readily, ketones are normally inert under the catalytic conditions.

Chiral Lewis-basic catalysts (Figures 15.1 and 15.2), in particular phosphoramides **8**–**12** [9, 14c, 15b,c, 22–24], formamide **13** [17], pyridine *N,N′*-dioxides **17**,



Scheme 15.2



8 (≤ 65% ee, *R*)[9]

9 (≤ 56% ee, *S*)[22]

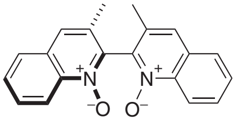
10 (≤ 72% ee, *R*)[14b,15c,22,23]

11 (≤ 72% ee, *S*)[22]

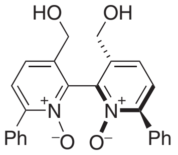
12 (≤ 87% ee, *S*)[22]

13 (≤ 98% ee, *R*)[17]

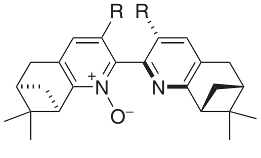
Figure 15.1 Examples of chiral Lewis-basic phosphoramide and formamide catalysts. The ee refers to the reaction of benzaldehyde with **2a**.



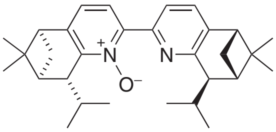
17 (88% ee, *R*)[25]



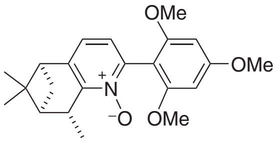
18 (84% ee, *S*)[26]



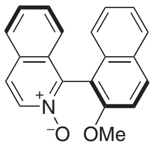
19, R = H (90% ee, *S*)[27]
20, R = Me (98% ee, *S*)[27]



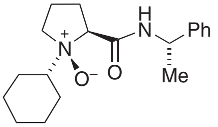
21 (97% ee, *S*)[27]



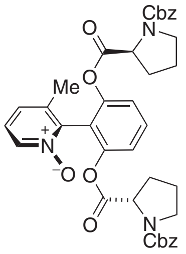
22 (96% ee, *S*)[28b]



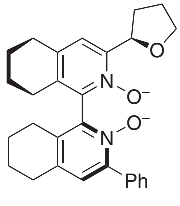
23 (89% ee, *R*)[30]



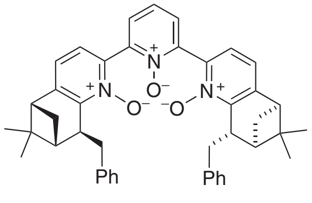
24 (87% ee, *R*)[31]



25 (68% ee, *S*)[32]



26 (96% ee, *S*)[36,37]



27 (86% ee, *R*)[33]

Figure 15.2 Further examples of chiral Lewis-basic *N*-oxide catalysts. The ee refers to the reaction of benzaldehyde with **2a**.

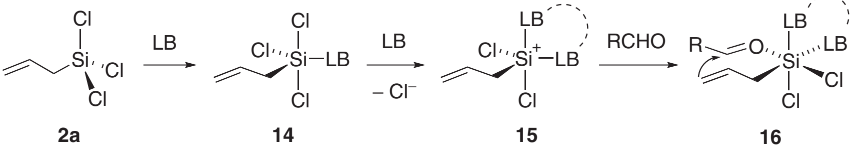
Table 15.1 Allylation benzaldehyde (**1**) with **2a-d**, catalyzed by phosphoramides at −78 °C (Scheme 15.1 and Figure 15.1) [9, 22].

Entry	Catalyst (mol%)	Silane	Yield (%)	*Syn:anti*	ee (%)
1	8 (10)	2a	40	–	53
2	**10** (25)	2a	59	–	72
3	**11** (5)	2a	58	–	72
4	**12** (5)	2a	85	–	87
5	**12** (5)	2b	82	1:99	86
6	**12** (5)	2c	89	99:1	94

and **18** [20, 25–27] and **26** [36, 37], *N*-monoxides (**19**–**25**) [20, 27–32], and *N,N′N″*-trioxides (**27**) [33] exhibit good to high enantioselectivities for the allylation of aromatic, heteroaromatic, and cinnamyl-type aldehydes (**1**) with allyl, *trans*- and *cis*-crotyl, and prenyl trichlorosilanes (**2a**–**d**). Chiral formamides (with the exception of **13** discussed below) [17], pyridine-oxazolines [34], urea derivatives [19], and sulfoxides [35] are effective only in stoichiometric quantities (or in excess) and, as a rule, exhibit lower enantioselectivities.

The early phosphoramides **8** and **9** (Figure 15.1), developed by Denmark [22], exhibited modest enantioselectivity in the allylation reaction (Scheme 15.1 and Table 15.1) but played an important role in the mechanistic elucidation and development of the second generation of catalysts (see below). The proline-derived phosphoramide **10** proved to be more selective (Table 15.1, entry 2) [14c, 15c] but its preparation is hampered by the fact that, unlike with **8** and **9**, its phosphorus atom is stereogenic, so that two diastereoisomers are formed and need to be separated. Phosphoramide **10** has been reported to give higher asymmetric induction than its diastereoisomer (entry 2) [22f]. However, the results are further affected by the variation of the N-substituents; generally, the sense of asymmetric induction appears to be independent of the configuration at the phosphorus, which only affects the level of enantiocontrol [22f]. The phosphoramides with a stereogenic phosphorus atom only provided up to 54% ee [22g].

Kinetic measurements and the observation of a nonlinear relationship between the enantiopurity of **8**/**9** and the product **3** led Denmark to the conclusion that two molecules of the catalyst are coordinated to the silicon center (**15**; Scheme 15.3)



Scheme 15.3

[22]. However, when the concentration of the catalyst is low, a second mechanism may compete, namely, that with only one molecule of the catalyst coordinated (**14**), which apparently attenuates the enantioselectivity [22]. Therefore, Denmark designed bidentate catalysts, such as **11** and **12**, which proved not only to exhibit higher enantioselectivities (Table 15.1; compare entries 1, 3, and 4) but also to react faster, so that their loading could be reduced from 10–20 to 5 mol% [22]. Excellent diastereoselectivity was observed for crotylation (entries 5 and 6), the sense of which is consistent with the transition state **5** discussed earlier (Scheme 15.2) [22f].

In addition to his synthetic work, Denmark carried out a very detailed investigation, using complexes of bis-phosphoramides **11** and **12** and their analogues, all with varying length of the tether connecting the two ligating units. Instead of Si, he employed Sn, which exhibits a similar coordination pattern but with stronger bonding, so that the complexes of Sn are more stable and can be studied. This switch to $SnCl_4$, in conjunction with ^{119}Sn and ^{31}P NMR and crystallographic studies, allowed him to confirm the bidentate, cis-coordination of the ligand, octahedral geometry of the Sn, and the details of the shape of the chiral cavity, dictated by the nature of the chiral scaffold and the length of the tether (with the optimum of five methylene units, as shown in **11** and **12**). Extrapolation of these findings to Si resulted in the formulation of a working mechanistic model for the allylation, and for the sense of asymmetric induction, presented in this chapter [22e]. Thus, ideally, in the transition state, the nucleophilicity of the allyl is increased by the trans-donation from the coordinated Lewis base, whereas the carbonyl of the aldehyde should be coordinated trans to the electron-withdrawing chloride – the site of maximal Lewis acidity, as shown in **16** [22e].

Chiral formamide **13** (Figure 15.1) typically requires ≥20 mol% loading and HMPA (1 equiv) as a co-catalyst; to attain 80% yield and 98% ee, the reaction was left at −78 °C for 2 weeks, which is less than practical. Interestingly, **13** is the only catalyst reported to date that exhibits very high enantioselectivities (≤98% ee) with aliphatic aldehydes, while with benzaldehydes it gives an almost racemic product (8% ee) [17].

Pyridine-type *N*-oxides (Figure 15.2) represent another, no less successful class of catalysts for the allylation reaction. Thus, Nakajima first demonstrated that the axially chiral biquinoline *N,N′*-dioxide **17** can indeed catalyze the allylation (Scheme 15.1) with high yield and enantioselectivity (71–92% ee at −78 °C) [25]. His efforts were later followed by Hayashi, who reported similar levels of asymmetric induction attained with the bipyridine analog **18** and its congeners (with 56–98% ee) [26]. Catalyst **18** is remarkably reactive, so that its loading can be reduced to the 0.1 mol% level, and moderate activity is retained even at 0.01 mol% loading [26], which renders **18** one of the most reactive organocatalyst reported to date. A chelation model, where both oxygens of the catalyst coordinate the silicon of the reagent, has been proposed [26] to account for the reactivity, mirroring the chelation model **16** suggested by Denmark for **11** and **12** [22].

Prior to Hayashi's report [26], Malkov and Kočovský [27] found the terpene-derived bipyridine *N*-monoxides **19**–**21** (PINDOX, Me_2PINDOX, and *iso*-PINDOX) to be even more enantioselective than Nakajima's *N,N′*-dioxide **17**, although the reaction rate dropped, especially with the severely hindered *iso*-PINDOX (**21**). The most successful derivative of this series, Me_2PINDOX (**20**), combines the effects of both central and axial chirality, since the rotation about the bond connecting the two pyridine moieties is restricted by the two methyls and the N–O group. However, the barrier to rotation is rather low and **20** isomerizes within several days (in solution) to a 1 : 2 mixture of **20** and its atropoisomer, which attenuates the asymmetric induction [27b]. PINDOX (**19**) and *iso*-PINDOX (**21**) lack the restriction to the rotation, so that a suitable configuration is apparently established on coordination to the silicon atom of the allylating reagent [27]. In analogy to the chelation model, proposed for **17** and **18**, chelation of the Si in $AllylSiCl_3$ by O and N was considered for **19–21** [27]. However, METHOX (**22**), lacking the pyridine ring, turned out to be much more reactive than **19–21** with the same level of enantioselectivity attained (≤96% ee at 1–5 mol% loading at −40 °C in MeCN) [28], suggesting that coordination to nitrogen in **19–21** may not play an important role. Instead, arene–arene interactions between the catalyst and the substrate have been suggested to account for the high reactivity and selectivity of the electron-rich **22** [28f, 28g, 29]. This hypothesis is supported by the lack of reactivity of the electron-poor analog with the 3,5-bis(trifluoromethyl)phenyl group in place of the 2,4,6-trimethoxyphenyl moiety of METHOX [28f, 28g]. Furthermore, the case of METHOX (**22**) shows clearly that the axial chirality, whether predetermined (as in **17** and **18**) or induced during the reaction (**19** and **21**), is not an absolute prerequisite for attaining high enantioselectivity in the allylation reaction [28]. Significantly, METHOX (**22**) has been shown to perform well not only with aromatic but also with α,β-unsaturated aldehydes (≤96% ee) [28d, 28e]. However, aliphatic (non-conjugated) aldehydes exhibit low enantioselectivities, demonstrating the importance of an adjacent π-system [28f, 28g].

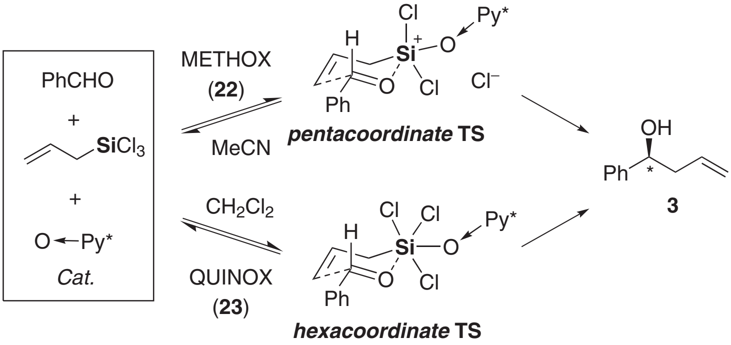
Other pyridine-type *N*-monoxides, namely, **23** (QUINOX) [30], **24** (the first non-pyridine-type *N*-oxide) and its congeners [31], and the pyridine *N*-oxide **25** [32] have also been reported as successful organocatalysts. This series is complemented by the *N,N′*-dioxide **26** (with ≤96% ee), its atropoisomer and their congeners [36, 37], the *N,N′,N″*-trioxide **27** and its analogues [33], and the related bis-imidazole *N,N′*-dioxides [38].

The effect of the electronic properties of the substituted benzaldehydes (**1a-c**) on the allylation reaction is another interesting issue. While most catalysts shown in Figures 15.1 and 15.2 generally exhibit a rather minor variation in ee (typically with less than 20% difference between the electron-rich and electron-poor aldehydes), METHOX (**22**) appears to be a particularly tolerant catalyst, exhibiting practically the same enantioselectivity (93–96% ee; Table 15.2, entries 1–3) and reaction rate across a range of substrates [28f, 28g]. In contrast, QUINOX (**23**) stands at the opposite side of the spectrum, showing the most dramatic differences between the electron-rich and electron-poor substrate aldehyde (16–96% ee; entries 4–6) [30]. Kinetic and computational studies shed some light on the latter behavior: it seems that METHOX prefers an ionic transition state with a pentacoordinate silicon (Scheme 15.4), whereas QUINOX favors the neutral, hexacoordinate species. This hypothesis is, *inter alia*, supported by the choice of solvents, namely,

Table 15.2 Electronic effects in the allylation of *p*-substituted benzaldehydes **1a–c** with **2a**, catalyzed by pyridine *N*-oxides **22** and **23** at −40 °C (Scheme 15.1 and Figure 15.2) [28, 30].

Entry	Catalyst	Aldehyde	R	Solvent	Yield (%)	ee (%)
1	22	1a	C_6H_5	MeCN	≥95	96
2	22	1b	4-$MeOC_6H_4$	MeCN	≥95	96
3	22	1c	4-$CF_3C_6H_4$	MeCN	86	93
4	23	1a	C_6H_5	CH_2Cl_2	60	87
5	23	1b	4-$MeOC_6H_4$	CH_2Cl_2	70	16
6	23	1c	4-$CF_3C_6H_4$	CH_2Cl_2	85	96

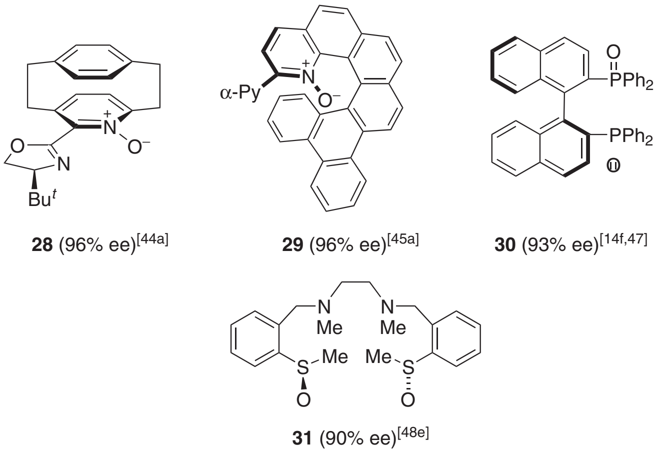
the polar acetonitrile in the former instance and non-polar dichloromethane in the latter [28f, 28g, 30b].



Scheme 15.4

Crotylation catalyzed by the *N*-oxides **17–23** [25–30] (and also by phosphoramides **8–12** [22]) is highly diastereoselective, with the *trans*-isomer **2b** affording almost exclusively the *anti*-product **3b**, while the *cis*-isomer **2c** gives mostly the *syn*-product **3c** (although in a slightly slower reaction). This behavior is consistent with the cyclic transition state **5** (Scheme 15.2) that guarantees a high degree of stereocontrol. METHOX (**22**) represents an extreme case, as it reacts well only with **2b**, affording **3b** with excellent diastereocontrol (>99 : 1) and enantioselectivity (95% ee), while the reaction with **2c** is very slow and less diastereoselective (6 : 1) [28b]. As a result, crotylation with an 83 : 17 (*E*/*Z*) mixture of (Crotyl)$SiCl_3$ (obtained from technical crotyl chloride and used in ≥1.5-fold excess), catalyzed by METHOX, affords pure *anti*-isomer **3b** (≥99 : 1 dr) [28b–d, 28g]. By contrast, QINOX (**23**) has been shown to exhibit lower diastereocontrol [30], which is due to its kinetic preference towards *cis*-(Crotyl)$SiCl_3$ [30b, 39].

Other pyridine-type *N*-oxides with various scaffolds (terpene [40], carbohydrate [41], etc. [42, 43]) have also been reported but as a rule their enantioselectivities do not exceeds those discussed above. A notable exception has been reported for

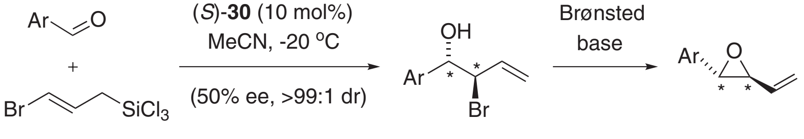


28 (96% ee)[44a] **29** (96% ee)[45a] **30** (93% ee)[14f,47] **31** (90% ee)[48e]

Figure 15.3 Examples of paracyclophanes (**28**), helicenes (**29**), phosphine oxides (**30**), and sulfoxides (**31**) employed as Lewis bases.

the paracyclophanes and helicenes, such as **28** (with ≤96% ee at 1.5 mol% loading) [44] and **29** (≤96% ee for propargylation with allenyltrichlorosilane at 10 mol% loading) [45] (Figure 15.3). Among other Lewis-basic catalysts that have been added recently to the mosaic are the phosphine oxides [46], such as BINAPO (**30**) with ≤93% ee [14f, 47]. Various sulfoxides [35, 48], for example, **31** [48e], and sulfinamides [49] also promote the allylation but only **31** works as a catalyst (at 30 mol% loading) [48e], whereas its congeners typically require more than stoichiometric amounts [50].

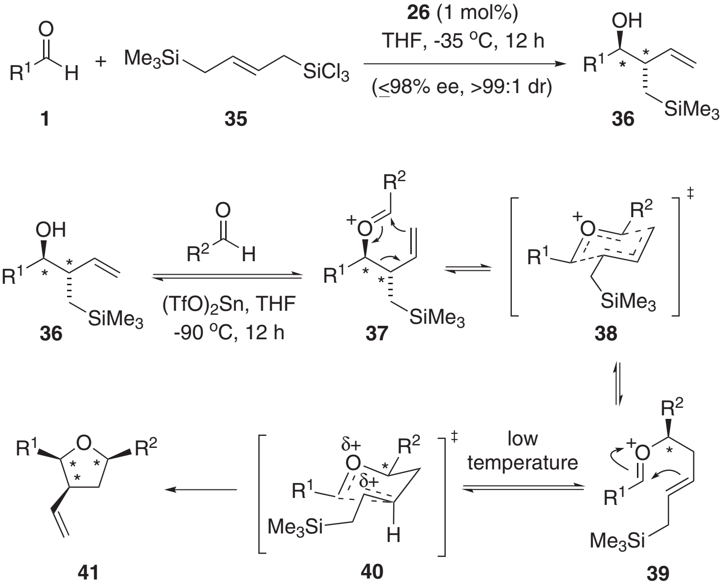
Aside from the simple allylation and crotylation, other substituted allylic derivatives have been investigated as well. Thus, the vinyl bromide **32** was reported by Malkov and Kočovský to produce bromohydrin **33** in modest enantioselectivity and excellent diastereoselectivity. BINAP (**30**) proved to be the best catalyst (Scheme 15.5), whereas other compounds, including METHOX (**22**) and QUINOX (**23**), gave inferior results. The bromohydrins thus formed were converted into the corresponding epoxides **34** upon treatment with NaH and other Brønsted bases [14f].



32 **33** **34**

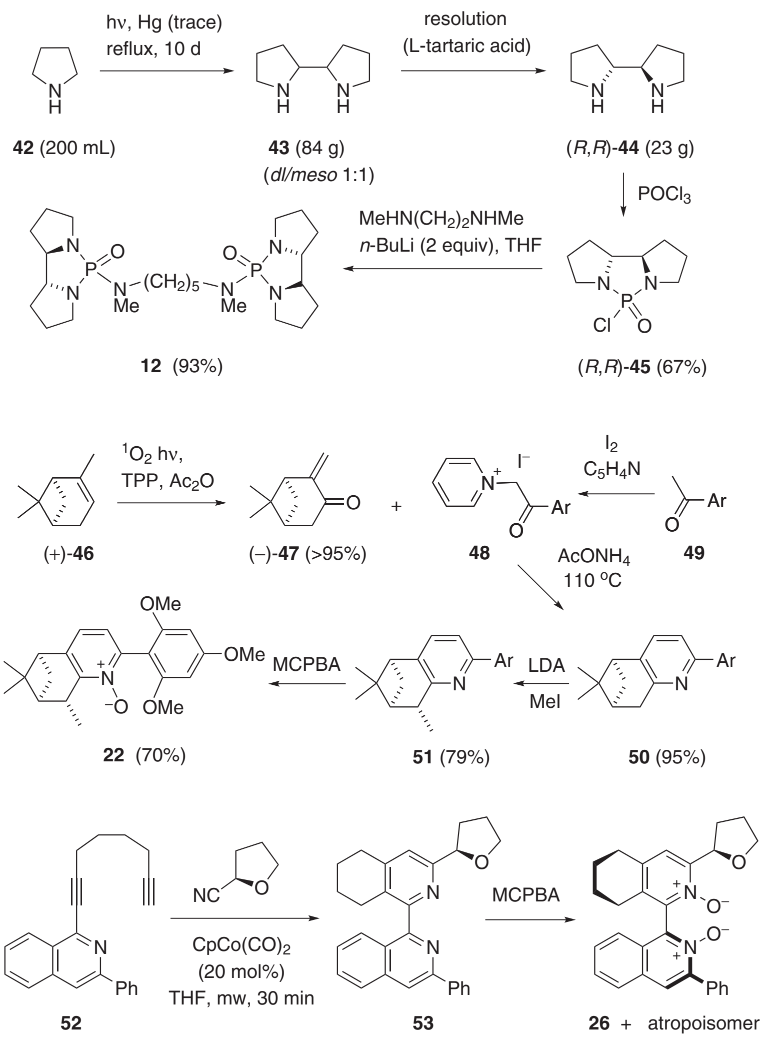
Scheme 15.5

1-Trichlorosilyl-4-trimethylsilyl-2-butene (**35**) represents a potentially bis-allylic system with an orthogonal reactivity of the two moieties (Scheme 15.6). Indeed, allylation of various aromatic and α,β-unsaturated aldehydes **1** with the latter reagent, catalyzed by METHOX (**22**) and QUINOX (**23**), afforded the expected homoallylic alcohol **36** in high stereocontrol (≤97% ee and ≥99 : 1 dr). However, the reaction takes 7–10 days, which is less than practical for industrial purposes. Employing the more reactive *N,N′*-dioxide **26**, originally developed by Kotora [36, 37], shortened the reaction time to 12 h, leaving the stereocontrol at the same level (≤98% ee and ≥99 : 1 dr) [14e]. Reaction of the product **36** with another aldehyde, catalyzed by $(TfO)_2Sn$ and other Lewis acids [14e, 28c], triggered a cascade including the formation of the oxonium ion **37**, whose [3,3]-sigmatropic rearrangement via **38** generated another oxonium ion (**39**) with a new allylsilane moiety, which proved to be a perfect substrate for the final intramolecular allylation. At −90 °C the resulting trisubstituted tetrahydrofurans **41** were obtained in ≤25 : 1 diastereoselectivity and preserved enantiopurity [14e].



Scheme 15.6

Of the catalysts listed in Figures 15.1 and 15.2, **12**, **18**, **22**, and **26** are the most efficient in terms of diastereo- and enantioselectivity, catalyst loading, and reaction rate. While **18** is synthesized in seven steps (including resolution or the use of a chiral auxiliary) [26], the other three are accessible in a more straightforward way. Thus, phosphoramide **12** was prepared in four steps (including resolution) from pyrrolidine (**42**) (Scheme 15.7) [22f]. The key step here is the photochemical dimerization of pyrrolidine (**42** → **43**), originally reported by Crabtree [51].

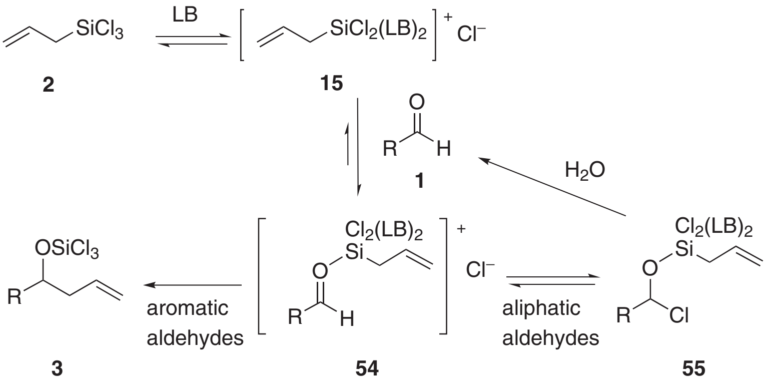


Scheme 15.7

METHOX (**22**) was synthesized in three steps from the commercially available pinocarvone (**47**) using the Kröhnke annulation (**47** + **48** → **50**). Pinocarvone itself, commercially available only in one enantiomeric form, can be readily obtained from the much cheaper α-pinene (**46**) via an ene-reaction with singlet oxygen. Since both enantiomers of α-pinene are commercially available, this procedure can be utilized for the preparation of both enantiomers of METHOX (**22**) [28b]. The Kröhnke reagent **48** [52] is readily obtained in one pot via iodination of the corresponding acetophenone (**49**) in pyridine [28b].

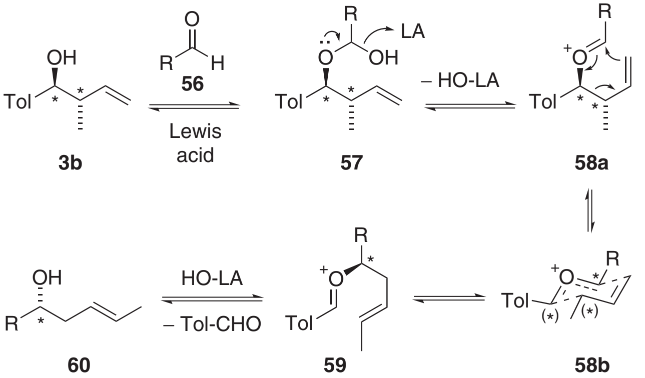
The axially chiral catalyst **26** was prepared by construction of the heterocyclic ring via a cobalt-catalyzed [2+2+2] cycloaddition of diyne **52** and the enantiopure, commercially available α-cyanotetrahydrofuran, followed by N-oxidation of the resulting bipyridine **53** with *m*-chloroperoxybenzoic acid (MCPBA), and a chromatographic separation of the two atropoisomers [36, 37]. The disadvantage of this synthesis are the rather low yields of the two key steps.

While aromatic, heteroaromatic, and α,β-unsaturated aldehydes react readily (to give 1,2-addition products in the latter case) [8, 12, 27–30, 36g, 37a], aliphatic aldehydes have been known to react sluggishly and to require stoichiometric conditions (see below). This problem has been addressed by Denmark (Scheme 15.8), who showed that instead of allylation, aliphatic aldehydes preferentially undergo a reaction with Cl^- as the nucleophile, while the oxygen is silylated (**15** → **54** → **3**). The unstable chlorosilyloxy derivative **55**, generated from aliphatic aldehydes, is then hydrolyzed on workup to regenerate the staring aldehyde **1** – a result that had been previously interpreted as if no reaction had occurred at all. To close the latter pathway, Denmark used various metal cations, in particular Hg^{2+}, which sequestered Cl^- [53]. Adding $HgCl_2$ (10 mol%) to a mixture of $PhCH_2CH_2CH{=}O$, **2a**, and catalyst **12** (5 mol%) in CH_2Cl_2 proved sufficient to reach 56% conversion at room temperature in 2 h. At −25 °C, the yield dropped to 32% and the enantioselectivity observed was 11% ee. Similarly, $HgCl_2$ had an accelerating effect on the allylation of benzaldehyde catalyzed by **12** but the product turned out to be racemic [53]. Hence, although promising, this protocol will require a fair amount of further development before it can become practical.



Scheme 15.8

The failure to attain good enantioselectivities in the catalytic allylation of aliphatic aldehydes lacking a π-system conjugated with the carbonyl has been partly amended by Malkov and Kočovský (Scheme 15.9) [28c]. According to their strategy, the enantiopure homoallylic alcohol **3b**, which in turn was obtained by the initial crotylation of tolualdehyde, is treated with an aliphatic aldehyde **56** in the presence of a Lewis acid, such as $(TfO)_3Sn$, to afford the homoallylic alcohol **60**. This cascade process can be rationalized by the initial formation of hemiacetal **57**, whose reaction with the Lewis (or even Brønsted) acid generates the oxonium ion **58a** that undergoes a sigmatropic rearrangement to generate another oxonium ion **59**, hydrolysis of which produces tolualdehyde and the new homoallylic alcohol **60**. A remarkable stereocontrol operates in this scheme, apparently via the chair-like transition state **58b**, where the two original chiral centers, highlighted as (*), are sacrificed at the expense of the formation of a new one and of the purely trans double bond. The system was optimized for the tolyl derivative **3b** as the tolyl group stabilizes the intermediate oxonium species **59** better than, for example, phenyl, which is the prerequisite for driving the cascade in the desired direction. Pertinently, the corresponding *p*-methoxy derivative, which could be anticipated to stabilize the oxonium species even better, proved unsuitable, as the substrate undergoes a ready dehydration, followed by polymerization [28c].



Scheme 15.9

Reaction of Allyltrichlorosilane (2a) with Benzaldehyde (1a) [28b]

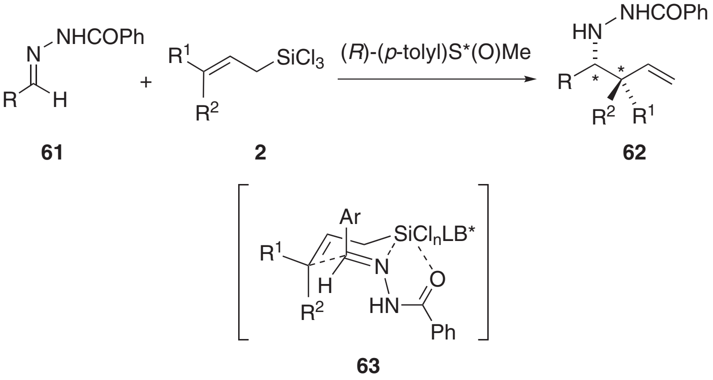
Allyl trichlorosilane (0.47 mmol) was added to a solution of METHOX (**22**) (0.02 mmol), diisopropylethylamine (2 mmol), and benzaldehyde (0.4 mmol) in acetonitrile (2 ml) under nitrogen at –40 °C. The mixture was stirred at the same temperature for 18 h and then the reaction was quenched with aqueous saturated. $NaHCO_3$ (1 ml). The aqueous layer was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash chromatography on a silica gel column (15 cm × 1 cm) with a petroleum ether–ethyl acetate mixture (95 : 5) to produce (*S*)-(–)-1-phenyl-but-3-en-1-ol (**3a**) (95%): chiral GC (Supelco β-DEX 120 column, oven: 100 °C for 5 min, then 1 °C min^{-1} to 200 °C, 10 min at that temperature) showed 96% ee (t_R = 31.06 min, t_S = 31.49 min).

15.2.2
Stoichiometric Allylation of Aldehydes and Ketones

As discussed above, catalytic allylation with $AllylSiCl_3$ is generally confined to conjugated aldehydes (aromatic, heteroaromatic, and cinnamyl). However, if a stoichiometric activator is employed, for example, DMF or HMPA, as an additive or solvent the substrate range broadens to aliphatic aldehydes and α-keto acids $RCOCO_2H$ (R = aryl, alkyl) [16]. In the case of chiral aldehydes, such as *N*-protected alaninal, diastereoselectivity attained in DMF is modest (~3 : 1) [54]. $AllylSiF_3$ can transfer the allyl group to α-hydroxy ketones and β-diketones on heating with Et_3N in THF [55].

Allylation of Imines and Hydrazones

N-Benzoyl hydrazones **61**, derived from aromatic and aliphatic aldehydes, undergo allylation with $AllylSiCl_3$ in DMF at 20 °C [56] or in CH_2Cl_2 with excess DMSO or Ph_3PO as activator at −78 °C (Scheme 15.10) [57]. Three equivalents(!) of (*R*)-(*p*-tolyl)S*(O)Me were required to induce the reaction of **61** (R = $PhCH_2CH_2$) with **2a**, which gave **62** in up to 93% ee [58]. Slightly higher reactivity has been reported for (*S*)-BINAPO (**30**), of which only 1 equivalent was required to effect the allylation of benzoyl hydrazone of ethyl glyoxylate, affording the corresponding (*R*)-product in up to 98% ee [59]. The allylation of hydrazones with (*E*/*Z*)-crotyl$SiCl_3$ exhibits the opposite diastereoselectivity to that observed for aldehydes, apparently owing to the different arrangement in the transition state (compare **63** with **5**) [56, 57, 60].



Scheme 15.10

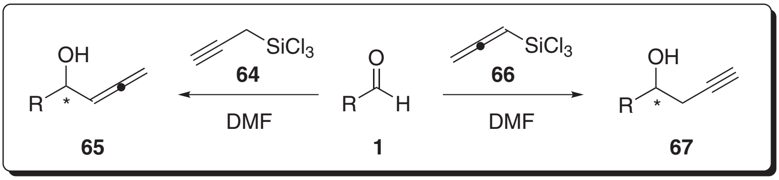
Allylation of hydrazones derived from aryl alkyl ketones [56] and of *N*-aryl aldimines in DMF at 0 °C [61] has also been reported.

Aldimines react with $AllylSiMe_3$ (**2a**) in the presence of iodine in MeCN to afford the products of allylation but an asymmetric version of this method has not yet been developed [62]. Nevertheless, with a chiral auxiliary attached to the imine nitrogen, dual catalysis was reported: here, In(III) was employed as a Lewis acid to coordinate the imine nitrogen, while $Bu_4N^+F^-$ was used as a Lewis basic activator of the Si, resulting in excellent diastereocontrol [63, 64].

15.3
Propargylation, Allenylation, and Addition of Acetylenes

15.3.1
Addition to Aldehydes

Reactions of propargyl trichlorosilane (**64**) with aromatic, heteroaromatic, and cinnamyl-type aldehydes (**1**), mediated by DMF (acting as a Lewis-base), have been shown to occur in analogy to the allylation, producing allenyl alcohols **65** with >99 : 1 selectivity (Scheme 15.11). Similarly, allenyl trichlorosilane (**66**) gives homopropargyl alcohols (**67**) [65, 66]. The reagents **64** and **66** were synthesized via a metal-catalyzed reaction of propargyl chloride with Cl_3SiH; with CuCl catalysis it leads to **64** (>99 : 1), whereas the reaction catalyzed by $(acac)_2Ni$ produced **66** (>99 : 1) [65]. The diastereoselectivity of these reactions has not yet been elucidated but its asymmetric version has been reported. Thus, using formamide **13** (20 mol%) and HMPA (1 equiv), Kobayashi was able to obtain **65** in up to 95% ee with pivalaldehyde as substrate (R = *t*-Bu), whereas less hindered aldehydes exhibited lower enantioselectivity (43–79% ee) [66c]. Interestingly, benzaldehyde gave (±)-**65** even if the catalyst loading was increased to 40 mol%. On the other hand, highly enantioselective formation of **67** (≤96% ee) has been reported for the helical pyridine *N*-oxide **29** as catalyst (at 10 mol% loading) [45].



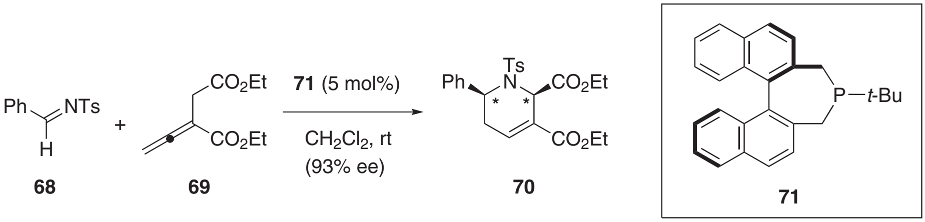
Scheme 15.11

Notably, unlike with other propargylic and allenic organometallics, no metallotropic interconversion of **64** and **66** has been observed, which points to an interesting potential of this methodology [65, 66].

An analogous propargylation can be attained with allenyl tributylstannane; however, this reaction is catalyzed by $SiCl_4$ that is activated by a bis-phosphoramide catalyst. Note that, in this case, the role of the Lewis basic phosphoramide is to increase the Lewis acidity of $SiCl_4$ rather than to increase the nucleophilicity of the stannane [66b]. For a discussion of these effects, see Section 15.4 .

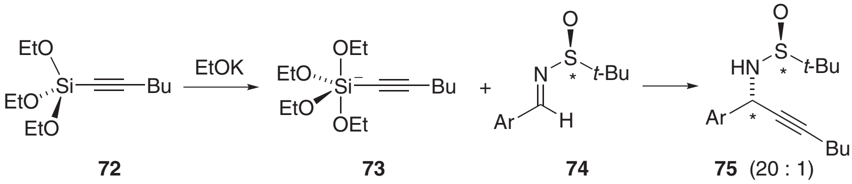
15.3.2
Addition to Imines

Allenylation of *N*-tosylimines, such as **68**, has been shown to effect the Kwon annulation with the allene derivative **69** on catalysis with the axially chiral phosphine **71** (Scheme 15.12). The piperidine derivative **70** were formed with good diastereocontrol (9 : 1) and high enantioselectivity (93% ee) [67, 68].



Scheme 15.12

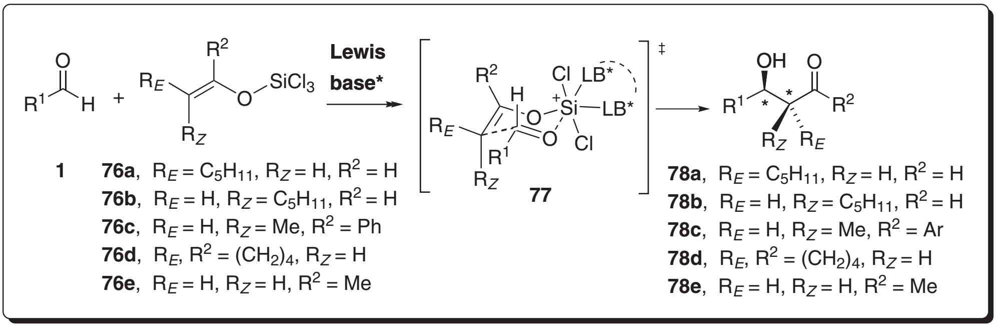
Triethoxysilyl acetylene (**72**) allows a new organocatalytic approach towards the introduction of the alkyne moiety (Scheme 15.13) via a nucleophilic addition to aromatic aldehydes, ketones, and aldimines, with EtOK as catalyst (10 mol%). Although a catalytic asymmetric version has not been developed to date, application of a chiral auxiliary, as in the case of imines **74**, led to the formation of **75** in an impressively high diastereoselectivity (20 : 1) [69], unparalleled by other acetylenic organometallics.



Scheme 15.13

15.4
Aldol-Type Reactions

According to Mayr's nucleophilicity scale (*N*), silyl enol ethers derived from aldehydes ($N \geq 3.5$) and ketones ($N \geq 5$) and, in particular, silyl ketene acetals ($N \geq 8$) [70] represent powerful nucleophilic reagents. Indeed, the aldol-type addition of trichlorosilyl enol ethers **76a–d** to aldehydes **1** proceeds readily at room temperature without a catalyst (Scheme 15.14), which is in contrast with the lack of reactivity of allyl silanes in the absence of a catalyst. As a result, the reaction exhibits simple first-order kinetics in each component [71, 72]. Nevertheless, the reaction is substantially accelerated by Lewis bases, which provides a solid ground for the development of an asymmetric variant. The required trichlorosilyl enol ethers **76** can be generated in various ways, for example: (i) from the corresponding trimethylsilyl enol ethers on reaction with $SiCl_4$, catalyzed by $(AcO)_2Hg$,


Lewis base*
‡
LB*
1
76a, $R_E = C_5H_{11}$, R_Z = H, R^2 = H
76b, R_E = H, $R_Z = C_5H_{11}$, R^2 = H
76c, R_E = H, R_Z = Me, R^2 = Ph
76d, R_E, $R^2 = (CH_2)_4$, R_Z = H
76e, R_E = H, R_Z = H, R^2 = Me
77
78a, $R_E = C_5H_{11}$, R_Z = H, R^2 = H
78b, R_E = H, $R_Z = C_5H_{11}$, R^2 = H
78c, R_E = H, R_Z = Me, R^2 = Ar
78d, R_E, $R^2 = (CH_2)_4$, R_Z = H
78e, R_E = H, R_Z = H, R^2 = Me

Scheme 15.14

(ii) from carbonyl compounds or trimethylsilyl enol ethers on treatment with Cl_3SiOTf, (iii) from α-chloroketones on reaction with Cl_3SiH and Et_3N, or (iv) from the corresponding tributylstannyl enol ethers, and so on [73] (for other approaches, see also Reference [76b]).

Denmark introduced an array of efficient chiral phosphoramides **79**–**81** as Lewis-basic activators (Figure 15.4) for the enantioselective C–C bond formation and also carried out a detailed mechanistic investigation [71, 74, 75]. Bidentate (e.g., **81**) and smaller monodentate catalysts (**79**) were shown to react via the cationic chair-like transition state **77** with octahedral hexacoordinate silicon (Scheme 15.14). Following this manifold, (*Z*)-enol ethers **76b** and **76c** produced *syn*-adducts **78b** and **78c**, whereas (*E*)-derivatives **76a** and **76d** furnished *anti*-diastereoisomers **78a** and **78d**. By contrast, with a bulky monodentate activator (e.g., **80**), where coordination of the second catalyst molecule is precluded by steric factors, the reaction exhibits opposite diastereoselectivity, presumably due to the cationic

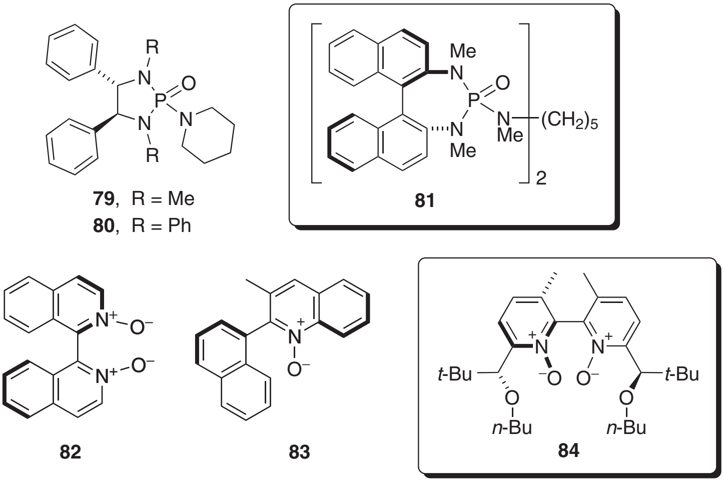


Figure 15.4 Chiral phosphoramides used as Lewis-basic activators (**79**–**81**) and chiral N-oxides (**82**–**84**).

Table 15.3 Aldol reaction (Scheme 15.14 and Figure 15.4) [5a, 75].

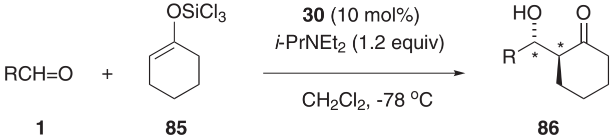
Entry	Catalyst	R^1	R^2	R_E	R_Z	Yield (%)	*Syn*:*anti*	ee (%)
1	**79**	Ph	Me	H	H	98	–	87
2	**79**	PhCH=CH	Bu	H	H	94	–	84
3	**79**	*c*-C_6H_{11}	-$(CH_2)_4$-		H	95	1:49	93
4	**79**	Ph	Ph	H	Me	95	18:1	95
5	**79**	Ph	Me	H	H	98	–	87
6	**81**	Ph	H	C_5H_{11}	H	91	3:97	82
7	**81**	Ph	H	H	C_5H_{11}	92	99:1	90

boat-like TS, where silicon is pentacoordinate. Along this manifold, cyclohexanone-derived enol ether **76d** with the fixed (*E*)-configuration of the double bond gave rise to the corresponding *syn*-product [71, 75]. Table 15.3 highlights some of the stereoselectivities.

The effect of a remote chiral center in this reaction has also been investigated. In most cases the reaction turned out to be controlled mainly by the chiral catalyst (e.g., **79**), whereas the resident center generally exercised a weak to modest influence [76].

Chiral *N*-oxides have also been employed as catalysts to promote aldol reactions [77] but their true potential remains to be realized. Catalysis by *N*-oxides follows the same general trends that were established for the phosphoramide activators, though with reduced enantioselectivity. Thus, Nakajima [77] has demonstrated that the reaction of aldehydes **1** with silyl enol ethers **76**, catalyzed by bidentate bis-*N*-oxides **17** and **82** [3 mol% of the catalyst, 1 equiv of $(i\text{-}Pr)_2NEt$, CH_2Cl_2, –78 °C], proceeds via TS **77**, resulting in high diastereoselectivity and moderate-to-good enantioselectivity (≤82% ee). On the other hand, aldol reaction of cyclic silyl enol ethers of type **76d** with aromatic aldehydes, catalyzed by bulky mono-oxides **23** and **83**, displayed *syn*-selectivity, which is consistent with participation of the boat-like TS. The enantioselectivity remained rather modest in the latter case (up to 72% ee) [77].

Nakajima has further shown that the enantio- and diastereoselective aldol reaction can be effectively catalyzed by BINAPO (**30**) in CH_2Cl_2 at –78 °C (Scheme 15.15). Thus, at 10 mol% catalyst loading and in the presence of *i*-$PrNEt_2$ (1.2 equiv), the reaction of the cyclohexanone-derived trichlorosilyl enol ether (**85**) with various aromatic, α,β-unsaturated, and aliphatic aldehydes **1** can reach up to 48 : 1 dr in favor of the *anti*-diastereoisomer **86** with up to 96% ee (Table 15.4) [78].

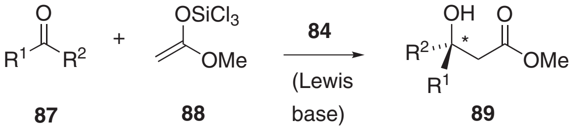


Scheme 15.15

Table 15.4 Aldol reaction of aldehydes **1** with silyl enol ether **85** catalyzed by **30** (Scheme 15.15) [78].

Entry	1, R^1	Time	Yield (%)	*Anti* : *syn*	ee (%)
1	Ph	25 min	94	14 : 1	87
2	(*E*)-PhCH=CH	30 min	83	7 : 1	81
3	$PhCH_2CH_2$	12 h	55	6 : 1	90
4	1-Naphthyl	25 min	97	34 : 1	55
5	2,4,6-$Me_3C_6H_5$	25 min	90	48 : 1	74
6	4-MeO–C_6H_4	25 min	96	6 : 1	78
7	4-NO_2–C_6H_4	25 min	90	25 : 1	96

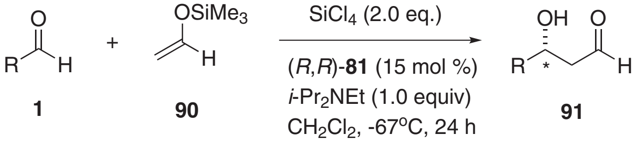
The range of substrates in the aldol reaction (and in allylation as shown above) employing trichlorosilyl reagents is generally restricted to aldehydes, while less reactive ketones remain essentially inert. However, the exceptionally high nucleophilicity of silyl ketene acetals [72] provides an opportunity to utilize ketones as substrates (Scheme 15.16). In the absence of an activator, addition of trichlorosilyl ketene acetal **88** to acetophenone (**87**, R^1 = Ph, R^2 = Me, Scheme 15.16) slowly takes place at 0 °C, paving the way for the development of a catalytic asymmetric variant. Among the large number of Lewis-basic promoters investigated, *N*,*N′*-dioxides emerged as the most promising class in terms of reactivity and enantioselectivity (cat. 10 mol%, −20 °C, CH_2Cl_2) [77, 79, 80]. Thus, bis-oxide (S_{ax},*R*,*R*)-**84**, with a matched combination of axial and central chirality, delivered the best results (≤86% ee), while its mismatched diastereoisomer furnished the opposite enantiomers of **89** with substantially reduced selectivities. Catalysts **17** and **82** also proved inferior [77].



Scheme 15.16

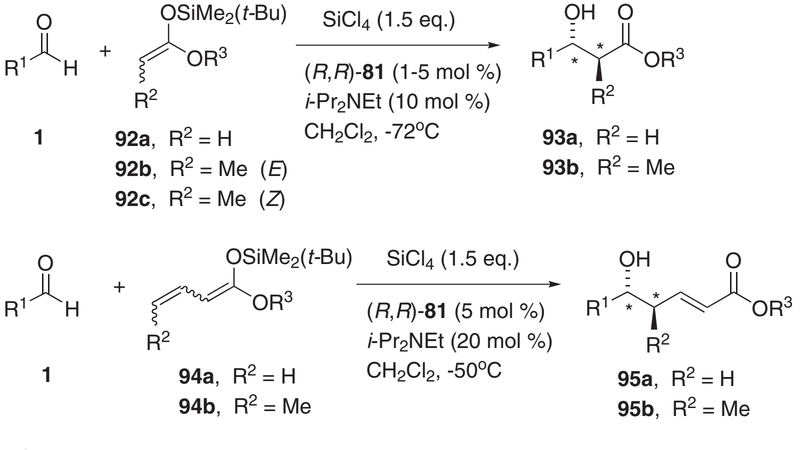
As a further reflection of their high nucleophilicity, silyl ketene acetals, such as **88**, proved to be reactive not only towards aromatic, heteroaromatic, and cinnamyl aldehydes but, very importantly, even to aliphatic aldehydes. Furthermore, the catalyst loading can be reduced to 1 mol% without erosion of enantioselectivity [80].

In stark contrast to trichlorosilyl enol ethers (**76** and **88**, etc.), their more readily obtainable trimethylsilyl counterparts, such as **90**, are insensitive to the presence of Lewis bases, owing to the lower Lewis acidity of the silicon atom. Therefore, a different approach was required if these nucleophiles were to be used in aldol chemistry. Here, Denmark turned to the well-established electrophilic activation of the aldehyde but in an interestingly innovative way. He employed $SiCl_4$, which itself is too weak a Lewis acid to promote the reaction. However, its coordination to a suitable Lewis base generates a new species that is sufficiently Lewis-acidic (see below) to facilitate the aldol reaction. Since only the activated species is reactive, the Lewis base can be used in a catalytic amount. Again, as the Lewis base, Denmark used a portfolio of phosphoramides, of which **81** turned out to be optimal (Scheme 15.17). With the latter catalyst (15 mol%) and with a suprastoichiometric amount of $SiCl_4$ (2 equiv), the reaction of aromatic aldehydes (**1**, R = aryl, cinnamyl) with the acetaldehyde-derived silyl enol ether **90** proceeded readily to afford the corresponding aldol adducts **91** in good yields and with high enantioselectivity (≤94% ee) [81, 82]. When bulkier trialkylsilyl groups (Ph_2MeSi or t-$BuMe_2Si$) or aliphatic aldehydes (R = Bu) were employed, the reaction was found not to proceed [81, 82].



Scheme 15.17

Trimethylsilyl ketene acetals **92** react in a similar way (note that a bulky trialkylsilyl group works well); ketene acetals derived from t-Bu esters proved to exhibit slightly higher enantioselectivities than their Me, Et, or Ph counterparts (Scheme 15.18 and Table 15.5) [83]. Owing to the higher reactivity of ketene acetals, the catalyst loading could be reduced to 1–5 mol%. However, in contrast to the trichlorosilyl enolates, this reaction is believed to proceed via an open transition state, since both (*E*) and (*Z*) isomers **92b**,**c** produce *anti*-aldol adducts **93** with high diastereo- and enantioselectivity (Scheme 15.18 and Table 15.6) [83].



Scheme 15.18

Table 15.5 Aldol-type reaction of aldehydes **1** with silyl ketenes **92a** (R^2 = H, R^3 = Me), catalyzed by **81** (Scheme 15.18) [83].

Entry	R^1	Yield (%)	ee (%)
1	Ph	97	86
2	(*E*) PhCH=CH	95	94
3	(*E*) PhCH=CH(Me)	98	45
4	2-Furyl	94	87
5	*c*-C_6H_{11}	86	88
6	$PhCH_2CH_2$	72	81

Table 15.6 Aldol-type reaction of aldehydes **1** with silyl ketenes **92b/92c** (R^2 = Me, R^3 = *t*-Bu) catalyzed by **81** (Scheme 15.18) [83].

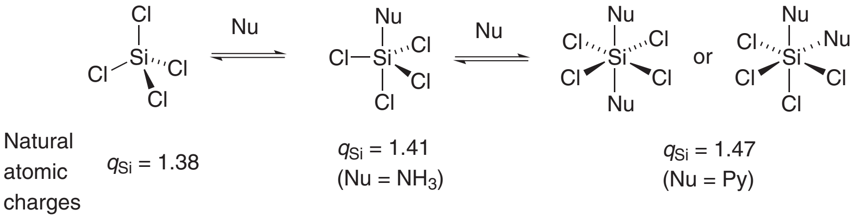
Entry	R^1	92b/c (***E*:*Z***)	Yield (%)	***Anti*:*syn***	ee (%)
1	Ph	**92b** (95:5)	93	≥99:1	100
2	Ph	**92b** (12:88)	73	≥99:1	99
3	(*E*) PhCH=CH	**92b** (95:5)	98	≥99:1	100
4	(*E*) PhCH=CH(Me)	**92b** (95:5)	90	≥99:1	92
5	*c*-C_6H_{11}	**92b** (95:5)	49	89:11	36
6	$PhCH_2CH_2$	**92b** (95:5)	55	93:7	89

Table 15.7 Aldol-type reaction of aldehydes **1** with vinylogous silyl ketenes **94a/94b** (R^3 = *t*-Bu) catalyzed by **81** (Scheme 15.18) [83].

Entry	R^1	R^2	Yield (%)	***Anti*:*syn***	ee (%)
1	Ph	H, **94a**	89	–	98
2	(*E*) PhCH=CH	H, **94a**	84	–	97
3	$PhCH_2CH_2$	H, **94a**	68	–	90
4	Ph	Me, **94b**	92	≥99:1	89
5	(*E*) PhCH=CH	Me, **94b**	71	≥99:1	82
6	$PhCH_2CH_2$	Me, **94b**	–	Not determined	Not determined

Vinylogous aldol-type reaction [83, 84] of aromatic and heteroaromatic aldehydes with silyl dienol ethers **94**, derived from α,β-unsaturated esters, also proceeded smoothly, furnishing exclusively the γ-addition products **95** (≥99:1) with high enantioselectivity (Scheme 15.18 and Table 15.7) [83b]. This reaction has also been reported for vinylogous amide analogues of **94** [83c].

The latter activation of Si with a Lewis base requires several comments: Computational analysis [85] revealed that silanes behave like weak Lewis acids towards neutral N- and O-donor Lewis bases. The equilibrium (Scheme 15.19) is greatly shifted to the left, that is, toward tetracoordinate silanes, but stronger Lewis bases or stabilizing intermolecular forces in the solution can enhance the formation of extracoordinate adducts [3e]. When a Lewis base is employed in catalytic quantity, the instability of the latter adduct should be viewed as a positive factor, because this effect can facilitate the catalyst turnover.



Scheme 15.19

Another important feature of the extracoordinate silicon compounds (Scheme 15.19) is the increase of the natural atomic charge at the central atom compared to the tetracoordinate precursors [85]. The counter-intuitive increase of the positive charge on silicon, which becomes even more substantial in the case of anionic nucleophiles, such as F^-, is compensated by a more negative character of the surrounding groups (X), which results in an enhanced ionic nature of the Si–X bond. This polarization then favors intermolecular charge–dipole interaction, which results in an increased Lewis acidity of the hypercoordinate silicon [86].

Trichloro[(1-phenylethenyl)oxy]silane (76e) [73c]

Silicon tetrachloride (9.18 ml, 80.0 mmol, 2.0 equiv) was added quickly to a suspension of $(AcO)_2Hg$ (127.0 mg, 0.40 mmol, 0.01 equiv) in CH_2Cl_2 (40 ml). During the addition, the mercury salt dissolved. Silyl enol ether derived from acetophenone (7.70 g, 40.0 mmol) was then added to the solution dropwise over 10 min, and the solution was stirred at room temperature for an additional 2 h. During this time, the reaction mixture became somewhat cloudy once again. Removal of an aliquot and ^1H NMR analysis indicated that the reaction was complete. The mixture was concentrated at reduced pressure (100 mmHg), and the resulting oil was distilled twice through a 7.5-cm Vigreux column to afford $CH_2{=}C(OSiCl_3)Ph$ **76e** (6.98 g, 69%) as a clear, colorless oil; upon storage (>1 d) this product turns deep yellow but this does not seem to affect the purity or reactivity: bp 85–87 °C (3 mmHg).

(*S*)-(–)-4-Hydroxy-4-phenyl-2-butanone [(*S*)-(–)-(78e)] [73b]

Trichloro[(1-methylethenyl)oxy]silane (**76e**) (421.3 mg, 2.2 mmol, 1.1 equiv) was added quickly to a cold (–74 °C) solution of (*S,S*)-**79** (37.3 mg, 0.1 mmol, 0.05 equiv) in CH_2Cl_2 (2 ml). A cold solution (–78 °C) of benzaldehyde (203 µl, 2.0 mmol) in CH_2Cl_2 (2 ml) was then added quickly via a short cannula; during the addition, the temperature rose to –67 °C. The reaction mixture was stirred at –75 °C for 2 h. The mixture was then quickly poured into a cold (0 °C) sat. aqueous solution of $NaHCO_3$ and the slurry was stirred for 15 min. The two-phase mixture was filtered through Celite, the phases separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on a column of silica gel with a mixture of pentane and ether (1 : 1) to furnish (*S*)-(–)-**78e** (R^1 = Ph) (321.6 mg, 98%) as a clear oil: $[\alpha]_D$ -51.4 (*c* 1.47, $CHCl_3$); chiral HPLC, carried out for the corresponding dinitrophenyl carbamate, revealed a 93.6 : 6.4 (*R*) : (*S*) ratio.

(*S*)-(-)-Methyl 3-Hydroxy-3-phenylbutanoate (89, R^1 = Ph, R^2 = Me) [79a]

Trichlorosilyl ketene acetal **88** (380 µl, 2.4 mmol, 1.2 equiv) was added to a solution of acetophenone **87** (PhCOMe) (240 µl, 2.0 mmol) and the bipyridine bis-*N*-oxide **84** (101 mg, 0.2 mmol. 0.1 equiv) in CH_2Cl_2 (10 ml) at –20 °C under nitrogen in a flame-dried, round-bottom flask with a magnetic stirrer. The mixture was stirred at –20 °C for 12 h and then transferred dropwise to an ice-cold saturated aqueous solution of $NaHCO_3$ (20 ml) with vigorous stirring. The mixture was further stirred at room temperature for 30 min. The silicate precipitate was filtered off through Celite and the filtrate was extracted with CH_2Cl_2 (4 × 20 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldol product was separated from the catalyst by distillation and then further purified by silica gel chromatography to afford (*S*)-(-)-**89**(R^1 = Ph, R^2 = Me). An analytically pure sample (364 mg, 94%) was obtained as a colorless liquid via Kugelrohr distillation: bp 110 °C ABT (1 mmHg); $[\alpha]_D$ –5.62 (*c* 1.09, EtOH); chiral HPLC (Chiracel OJ, 1.1% MeOH in CO_2, 150 bar, 40 °C, 2.5 ml min^{-1}) showed 82% ee [t_R = 2.85 min (8.7%), t_S = 3.04 min (91.2%)].

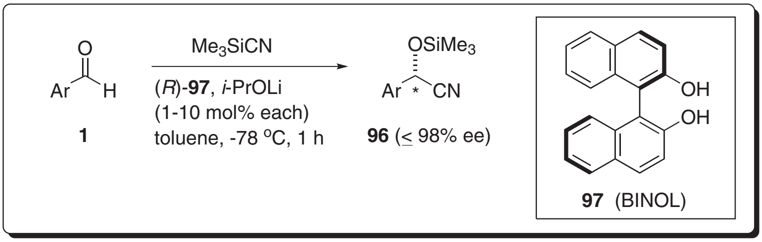
Methyl (*R*)-3-Hydroxy-3-phenylpropanoate (*R*)-(+)-93a (R^1 = Ph, R^2 = H, R^3 = Me) [83a]

Benzaldehyde (**1**, R = Ph) (100 µl, 2.0 mmol, 1.0 equiv) was added in one portion to a solution of bis-phosphoramide (*R,R*)-**81** (84 mg, 0.1 mmol, 0.05 equiv) at –78 °C under nitrogen in a flame-dried, round-bottom flask with a magnetic stirrer, followed by $SiCl_4$ (252 µl, 2.2 mmol, 1.1 equiv) and the mixture was stirred at –78 °C for 5 min. 1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethene **92a** (523 µl, 2.4 mmol, 1.2 equiv) was then added dropwise over a period of 5 min and the mixture was stirred for 15 min. The resultant cold mixture was poured into a rapidly stirred solution of sat. aqueous KF and 1.0 M KH_2PO_4 (1 : 1 mixture; 50 ml). The biphasic mixture was stirred vigorously for 2 h and then the aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on a column of silica gel with a mixture of hexanes and AcOEt (2 : 1) to afford (*R*)-(+)-**93a** (R^1 = Ph, R^2 = H, R^3 = Me) as a colorless oil (348 mg, 97%): $[\alpha]_D$ +17.7 (*c* 2.05, EtOH); chiral HPLC (Chiralpak AD, 3.5% MeOH in CO_2, 200 bar, 40 °C, 2.7 ml min^{-1}, 220 nm) showed 92.6% ee [t_R = 3.81 min (96.3%), t_S = 4.23 min (3.7%)].

15.5
Cyanation and Isonitrile Addition

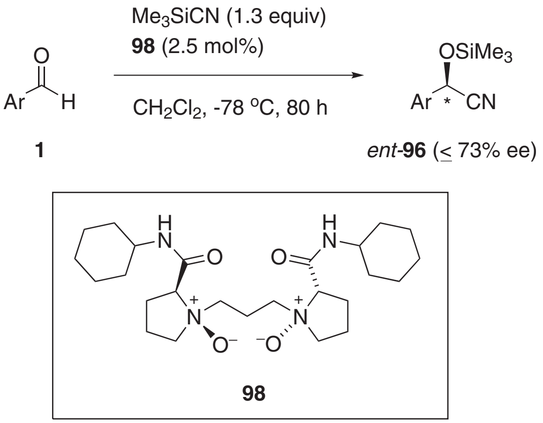
15.5.1
Cyanation of Aldehydes

Activation of Me_3SiCN by coordination of the Si to lithium BINOL-ate as catalyst has been shown to result in the enantioselective formation of cyanohydrins **96** from aromatic and heteroaromatic aldehydes with 82–98% ee (Scheme 15.20) [87]. Several other groups used dual activation with a chiral Lewis acid and a non-chiral Lewis base [88]. Asymmetric cyanosilylation of PhCOMe and its congeners has also been reported to occur in the presence of sodium phenyl glycinate as catalyst, with up to 94% ee [89].



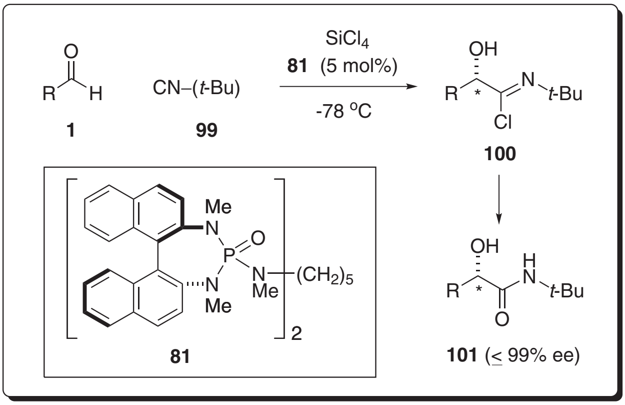
Scheme 15.20

The *N*,*N*′-dioxide **98** has been reported to catalyze the formation of TMS-cyanohydrins *ent*-**96** apparently without the need for dual activation (Scheme 15.21). However, the reaction requires a rather long time (80 h) to reach completion at acceptable enantioselectivity (≤73% ee) [90].



Scheme 15.21

A related reaction is the addition of isonitriles **99** to aldehydes **1** (Passerini reaction). Denmark has demonstrated that $SiCl_4$, upon activation by a chiral Lewis base, which increased the Lewis acidity of the silicon (see above; Scheme 15.19), can catalyze this reaction to produce α-hydroxy amides **101** after aqueous workup (Scheme 15.22). Phosphoramide **81** was employed as the chiral Lewis-basic catalyst [91]. Modification of the procedure for hydrolysis of **100** gives rise to the corresponding methyl ester (rather than amide **101**) [91].



Scheme 15.22

Catalytic Asymmetric Cyanation with (*R*)-BINOLi/-PrOLi (10 mol%) [87]

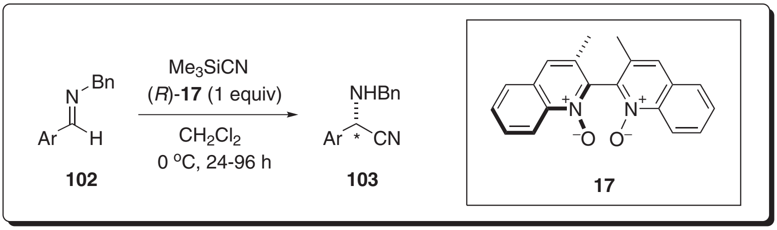
A mixture of (*R*)-BINOL (**97**) (28.6 mg, 0.1 mmol) and *i*-PrOLi (6.6 mg, 0.1 mmol) in toluene (2 ml) was stirred at room temperature for 20 min under a nitrogen atmosphere. Benzaldehyde (101.6 μl, 1.0 mmol) was then added and the mixture was stirred at room temperature for 20 min. This pale yellow solution was cooled to –78 °C and stirred for 10 min at that temperature. Trimethylsilyl cyanide [*Caution!*] (133.1 μl, 1.0 mmol) was added dropwise, and the mixture war stirred at –78 °C for 1 h. The mixture was then diluted with a 10% (w/w) solution of HCl in MeOH (1 ml) and stirred at –78 °C for 10 min. Water (10 ml) and ethyl acetate (10 ml) were then added and the product was extracted with ethyl acetate (2 × 10 ml), the combined organic phase was washed with brine (10 ml), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude cyanohydrin. The latter product was dissolved in dichloromethane (2 ml), cooled to –78 °C, and pyridine (0.16 ml, 2 mmol) and acetic anhydride (0.14 ml, 1.5 mmol) were added. The mixture was stirred at room temperature for 30 min and then diluted with ethyl acetate (20 ml) and 1M HCl (10 ml). The organic phase was separated, washed with water (10 ml), a saturated aqueous solution of $NaHCO_3$ (10 ml), and brine (10 ml) then dried over $MgSO_4$ and evaporated under reduced pressure to give the cyanohydrin acetate, which was purified by neutral silica gel column chromatography (hexane–AcOEt, 10 : 1) to afford the pure cyanohydrin acetate as a colorless oil (175.2 mg, >99%). The enantiomeric purity was determined by chiral GC using a CP-cyclodextrin-β-2,3,6-M-19 column [120 °C, $t_R = 23.8$ min, $t_S = 27.3$ min (major); 95% ee (*S*)].

***N-tert*-Butyl-2-hydroxy-2-(2-naphthyl)acetamide (*S*)-(+)-(101)** [91b]

A solution of *tert*-butyl isocyanide **99** (125 μl, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 ml) was added via a syringe pump over 4 h to a cold (–74 °C, internal temperature) solution of 2-naphthaldehyde (156 mg, 1.0 mmol), catalyst (*R*,*R*)-**81** (43 mg, 0.05 mmol, 0.05 equiv), $SiCl_4$ (125 μl, $d = 1.483$, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μl, $d = 0.742$, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 ml) in a two-necked, round-bottomed flask fitted with an argon inlet adapter and thermocouple. The mixture was stirred further at –74 °C for 4 h. The reaction mixture was then transferred dropwise to a vigorously stirred, ice-cold, saturated aqueous solution of $NaHCO_3$ (20 ml) and the resulting mixture was stirred at room temperature for 2 h. The white precipitate was filtered off through Celite and the filtrate was extracted with CH_2Cl_2 (4 × 20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (20 mm column, 60 g SiO_2, R_f 0.17, hexane–AcOEt, 3 : 1) to afford (*S*)-(+)-**101** (242 mg, 93%) as a white solid. An analytically pure sample was obtained after sublimation (90 °C at 0.5 mmHg): mp 94–96 °C (sublimed); SFC, $t_R = 3.73$ min (0.3%), $t_S = 4.58$ min (99.7%) (Chiracel AD, 10% MeOH in CO_2, 125 bar, 40 °C, 3.0 ml min^{-1}); $[\alpha]_D^{24}$ +44.9 (*c* 0.96, MeOH).

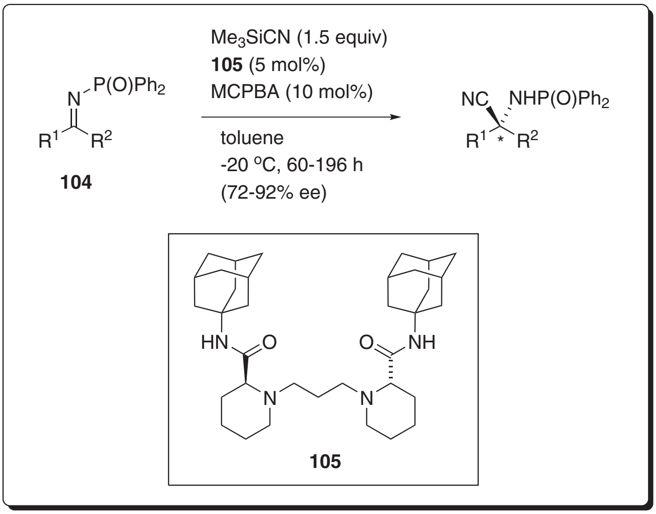
15.5.2
Cyanation of Imines (Strecker Reaction)

Axially chiral bis-isoquinoline *N,N′*-dioxide (*S*)-**17** has been reported to promote the addition of Me_3SiCN (1.5–2.0 equiv) to imines **102**, derived from aromatic aldehydes (Scheme 15.23); CH_2Cl_2 was identified as an optimal solvent. The reaction is stoichiometric in **17** and exhibits partial dependence on the imine electronics (62–78% ee), but much less so than that observed for the allylation of PhCHO catalyzed by QINOX (**23**) (see above). The *o*-substitution had a positive effect in the case of Cl (95% ee) but a very negative effect in the instance of MeO (12% ee). Chelation of the silicon by the *N*-oxide groups was suggested to account for the stereochemical outcome. Analogues of **17** were much less successful [92].



Scheme 15.23

A catalytic Strecker reaction (Scheme 15.24) has been developed, with **105** as a pre-catalyst, which is *in situ* converted into the corresponding *N,N′*-dioxide on



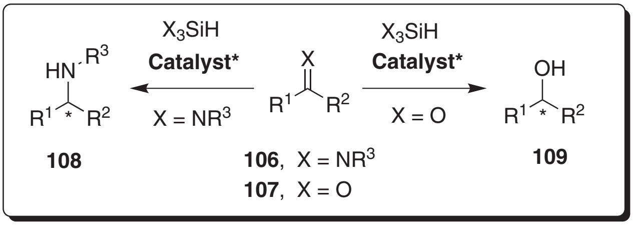
Scheme 15.24

reaction with *m*-chloroperoxybenzoic acid (2 equiv related to the amount of the pre-catalyst). With a range of aromatic *N*-diphenylphosphinoyl ketimine **106** the reaction exhibited ≤92% ee but at rather long reaction times [93].

The combination of Me_2AlCN and BINOL **97** (1.2 equiv) also induced the cyanation of imines derived from benzaldehyde, affording the Strecker products in up to 70% ee [94]. Finally, *N*-allylbenzaldimines have been reported to react with HCN in the presence of chiral ammonium salt catalysts [95, 96].

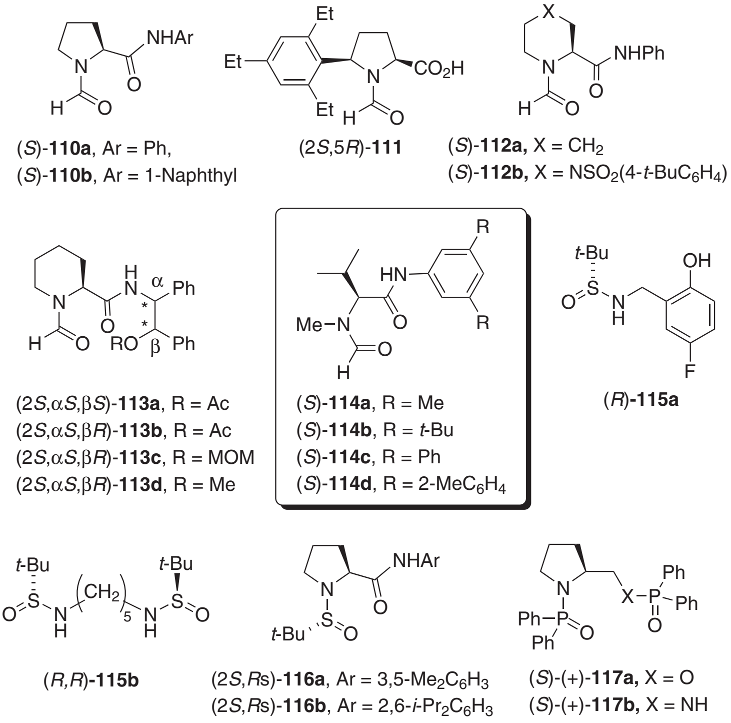
15.6
Reduction Reactions

Silanes are widely recognized as efficient reagents for reduction of carbonyl and heterocarbonyl functionality (Scheme 15.25). In the case of alkyl- and arylsilanes, the reaction requires catalysis by transition metal complexes [1]; however, with more Lewis-acidic trichloro- or trialkoxysilanes, an alternative metal-free activation can be accomplished [3]. It has been demonstrated that extracoordinate silicon hydrides, generated by coordination of silanes to Lewis bases, such as tertiary amines [3a] or DMF [3b], can serve as mild reagents for the reduction of imines to amines. In the case of trichlorosilane, an inexpensive and relatively easy-to-handle reducing reagent, and DMF acting as a Lewis base, the intermediacy of hexacoordinate species has been confirmed by ^{29}Si NMR spectroscopy [3b].



Scheme 15.25

Not surprisingly, chiral DMF analogues **110–114** [97, 98] (Figure 15.5) emerged as a first successful group of catalysts for the asymmetric hydrosilylation of ketimines, which sparked an exponential growth in the field and led to the appearance of a wide variety of new chiral Lewis bases capable of delivering high yields and high enantioselectivities in the reduction of ketimines [99]. Apart from the formamides, other major catalyst types are shown in Figures 15.1 and 15.2 and also include sulfinamides **115** and **116** [100], and phosphinic amides **117** [101], as well as a set of nitrogen Lewis bases, such as picolinamides **118–120** [102], the related imidazole derivative **121** [103], axially chiral bis-picolinamide **122** [104], and finally pyridyl oxazolines **123** and **124** [105] (Figure 15.6). Representative examples



(*S*)-**110a**, Ar = Ph,
(*S*)-**110b**, Ar = 1-Naphthyl

(2*S*,5*R*)-**111**

(*S*)-**112a,** X = CH_2
(*S*)-**112b,** X = NSO_2(4-*t*-BuC_6H_4)

(2*S*,α*S*,β*S*)-**113a**, R = Ac
(2*S*,α*S*,β*R*)-**113b**, R = Ac
(2*S*,α*S*,β*R*)-**113c**, R = MOM
(2*S*,α*S*,β*R*)-**113d**, R = Me

(*S*)-**114a**, R = Me
(*S*)-**114b**, R = *t*-Bu
(*S*)-**114c**, R = Ph
(*S*)-**114d**, R = 2-MeC_6H_4

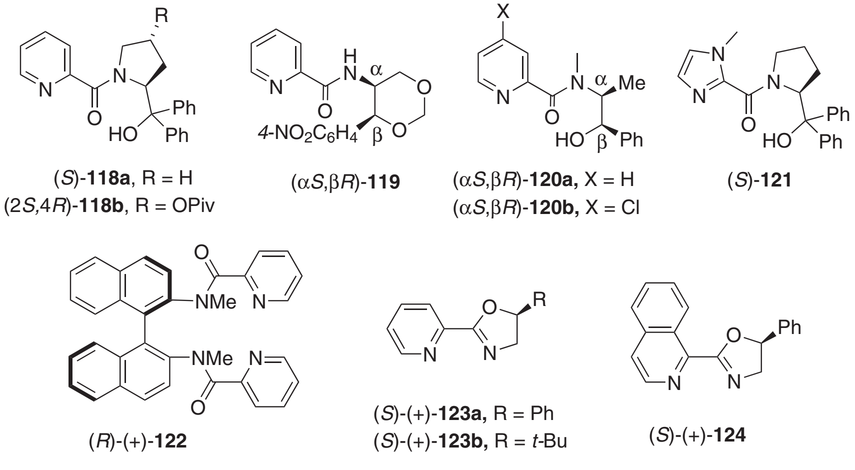
(*R*)**-115a**

(*R*,*R*)**-115b**

(2*S*,*R*s)-**116a**, Ar = 3,5-$Me_2C_6H_3$
(2*S*,*R*s)-**116b**, Ar = 2,6-*i*-$Pr_2C_6H_3$

(*S*)-(+)-**117a,** X = O
(*S*)-(+)-**117b,** X = NH

Figure 15.5 Formamides and related catalysts for asymmetric reduction of ketimines.



(*S*)-**118a**, R = H
(2*S*,4*R*)-**118b**, R = OPiv

(α*S*,β*R*)-**119**

(α*S*,β*R*)-**120a,** X = H
(α*S*,β*R*)-**120b,** X = Cl

(*S*)-**121**

(*R*)-(+)-**122**

(*S*)-(+)-**123a**, R = Ph
(*S*)-(+)-**123b,** R = *t*-Bu

(*S*)-(+)-**124**

Figure 15.6 Nitrogen Lewis bases used in the enantioselective reduction of ketimines.

Table 15.8 Asymmetric reduction of imines **106** derived from aromatic amines with trichlorosilanes catalyzed by chiral Lewis bases **110**, **112**–**115**, **118**, and **120**–**124** (Scheme 15.25 and Figures 15.5 and 15.6).

Entry	Imine R^1, R^2, R^3	Catalyst (mol%)	Solvent	Temperature (°C)	Yield (%)	ee (%) (config.)
1	**106a**, Ph, Me, Ph	(*S*)-**110a** (10)	CH_2Cl_2	Ambient	91	55 (*R*)
2	**106a**	(*S*)-**110b** (10)	CH_2Cl_2	Ambient	52	66 (*R*)
3	**106a**	(*S*)-**112a** (10)	CH_2Cl_2	0	94	73 (*R*)
4	**106a**	(*S*)-**112b** (10)	CH_2Cl_2	−20	95	89 (*R*)
5	**106a**	(*S*,*S*,*S*)-**113a** (10)	CH_2Cl_2	0	97	94 (*R*)
6	**106a**	(*S*,*S*,*R*)-**113b** (10)	CH_2Cl_2	0	97	93 (*R*)
7	**106b**, Ph, Me, *p*-methoxyphenyl (PMP)	(*S*)-**114a** (10)	Toluene	Ambient	85	91 (*S*)
8	**106b**	(*S*)-**114b** (5)	Toluene	Ambient	95	94 (*S*)
9	**106b**	(*S*)-**114c** (5)	Toluene	Ambient	92	73 (*S*)
10	**106b**	(*S*)-**114d** (5)	Toluene	Ambient	98	90 (*S*)
11	**106a**	(*R*)-**115a** (20)	CH_2Cl_2	−20	92	92 (*S*)
12	**106a**	(*R*,*R*)-**115b** (10)	CH_2Cl_2	−20	91	96 (*S*)
13	**106a**	(*S*)-**118a**	CH_2Cl_2	Ambient	86	73 (*S*)
14	**106a**	(*S*,*R*)-**120a** (20)	$CHCl_3$	−10	88	92 (*R*)
15	**106a**	(*S*)-**121** (1)	$CHCl_3$	0	81	86 (*S*)
16	**106a**	(*R*)-**122** (10)	CH_2Cl_2	0	99	75 (*R*)
17	**106a**	(*S*)-**123** (20)	$CHCl_3$	−20	94	54 (*R*)
18	**106a**	(*S*)-**124** (20)	$CHCl_3$	−20	65	87 (*R*)

of the enantioselective reduction of acetophenone-derived ketimines **106a** and **106b** are collected in Tables 15.8 and 15.9.

Proline-derived anilide **110a** and its naphthyl analog **110b** [3c], introduced by Matsumura, produced moderate enantioselectivity in the reduction of aromatic ketimines with trichlorosilane at 10 mol% catalyst loading (Table 15.8, entries 1 and 2). Replacing the rigid proline core with a more flexible pipecolinic acid fragment **112a** or its piperazine derivative **112b**, led to an increased selectivity (Table 15.8, entries 3 and 4) [98b,c]. Further improvement was attained with catalysts **113a,b**, where 1,2-diphenylamino-ethanol derivatives were used instead of aniline to form the amide (entries 5 and 6). In the latter catalysts, the configuration at the

Table 15.9 Asymmetric reduction of imines **106** derived from non-aromatic amines catalyzed by chiral Lewis bases **116**, **118**, and **120–122** (Scheme 15.25 and Figures 15.5 and 15.6).

Entry	Imine R^1, R^2, R^3	Catalyst (mol%)	Solvent	Temperature (°C)	Yield (%)	ee (%)
1	**106c**, Ph, Me, Bn	(*S*)-**116a** (10)	Toluene	0	98	96
2	**106d**, Ph, Me, *p*-methoxybenzyl (PMB)	(*S*)-**116a** (10)	Toluene	0	85	93
3	**106e**, Ph, Me, allyl	(*S*)-**116a** (10)	Toluene	0	82	92
4	**106e**, Ph, Me, *n*-Pr	(*S*)-**116a** (10)	CCl$_4$	0	60	90
5	**106c**	(*S*)-**118a** (10)	CH$_2$Cl$_2$	Ambient	67	80
6	**106c**	(*S,R*)-**120a** (20)	CHCl$_3$	–10	85	80
7	**106c**	(*S,R*)-**120b** (20)	CH$_2$Cl$_2$	0	98	80
8	**106c**	(*S*)-**121** (1)	CH$_2$Cl$_2$	0	63	80
9	**106c**	(*S*)-**122** (10)	CH$_2$Cl$_2$	0	99	87

α-carbon of the amino alcohol moiety proved to be critical for the formation of the matched pair, while configuration at the β-carbon had no influence on the enantioselectivity [98a].

An alternative approach to improve the catalyst design was taken by Malkov and Kočovský [97], who employed acyclic *N*-methyl amino acids in the core of the catalyst structure, as illustrated by catalysts **114a–114d** (Table 15.8, entries 7–10). Intrinsic rotational flexibility of the bond linking the stereogenic center to the formamide nitrogen allowed the molecule to adopt the most favorable conformation in the transition state. As a result, valine derived catalysts **114**, having a single chiral center, delivered a level of enantioselectivity similar to or higher than the more complex systems **113a,b**. Furthermore, despite the same configuration of the parent amino acids in **110–113**, the valine-based catalysts **114** induced the formation of the opposite enantiomer of the product (compare Table 15.8 entries 1–6 with entries 7–10). Of various amino acids, the valine framework emerged as the most efficient, the cyclohexyl and *t*-butyl (obtained from *tert*-leucine) analogues showed a marginally reduced efficiency, whereas modest to low enantioselectivities were observed for the phenylglycine-, phenylalanine-, and alanine-derived catalysts. On the other hand, the steric bulk of the anilide component proved to be the key to high enantioselectivity, where Sigamide **114b**, derived from 3,5-di-*tert*-butylaniline, was identified as optimum (≤94% ee with 1–5 mol% loading; Table 15.8, entry 8) [97b]. Furthermore, the commercially available valine-derived Kenamide **114a** and Sigamide **114b** are among the most versatile catalysts for the reduction of *N*-aryl ketimines, delivering high enantioselectivity over a broad substrate range, including imines derived from both aromatic and non-aromatic ketones [97e].

A different design of catalyst, featuring a Lewis-basic sulfinamide group as the chiral element, was introduced by Sun [100a]. Catalyst **115a** produced **108a** in 93% ee at –20 °C, though a hefty 20 mol% catalyst loading was required (Table 15.8, entry 11). The analogous bis-sulfinamide **115b** (10 mol%), in combination with 30 mol% of 2,6-lutidine, exhibited increased enantioselectivities (96% ee at –20 °C; Table 15.8, entry 12) [100c].

The proline motif was rekindled by Matsumura, who modified the original structure of **110a** by replacing the formamide group with picolinoylamide and the anilide moiety with a diphenylcarbinol segment [102a]. The new catalyst **118a** thus obtained exhibited increased enantioselectivities and, compared to **110a**, induced the opposite configuration of the products (Table 15.8, entry 13). However, the most essential feature of **118a** is its efficiency with ketimines derived from both aromatic and non-aromatic amines (Table 15.8, entry 13 and Table 15.9, entry 5). Later, several other catalysts, such as **120–122**, were shown to share this ability (Table 15.8 entries 14–16 and Table 15.9, entries 6–9). For the imines, derived from nonaromatic amines, sulfinamides **116** proved to be the most efficient catalyst, consistently showing high enantioselectivities (Table 15.9, entries 1–4). Naturally, this feature further expands the scope of asymmetric hydrosilylation of ketimines and opens up new synthetic opportunities.

In an earlier report, Matsumura revealed that, apart from the imines, catalyst **110b** also showed modest selectivities in the reduction of ketones (≤51% ee; Table 15.10, entries 1, 2) [3c]. Enantioselectivity in this reaction was greatly improved by the introduction (by the same group) of formamide **111** derived from 5-arylproline, which allowed benzylic alcohols **109** to be obtained in high enantiomeric purity (Table 15.10, entries 3–5) [98h]. In parallel, Malkov and Kočovský introduced a

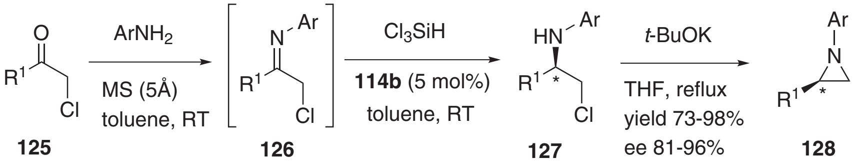
Table 15.10 Asymmetric reduction of ketones **107** with trichlorosilanes catalyzed by chiral Lewis bases (Scheme 15.25 and Figures 15.5 and 15.6).

Entry	Ketone R^1, R^2	Catalyst (mol%)	Solvent	Temperature (°C)	Yield (%)	ee (%) (config.)
1	**107a**, Ph, Me	(*S*)-**110b** (10)	CH_2Cl_2	0	79	43 (*R*)
2	**107b**, Ph, CH_2Ph	(*S*)-**110b** (10)	CH_2Cl_2	0	27	51 (*R*)
3	**107a**	(*S*,*R*)-**111** (3)	$CHCl_3$	Ambient	90	95 (*R*)
4	**107c**, Ph, *n*-Pr	(*S*,*R*)-**111** (3)	$CHCl_3$	Ambient	90	95 (*R*)
5	**107d**, 2-MeC_6H_4, Me	(*S*,*R*)-**111** (3)	$CHCl_3$	Ambient	91	96 (*R*)
6	**107a**	(*S*)-**123** (20)	$CHCl_3$	–20	85	78 (*R*)
7	**107a**	(*S*)-**124** (10)	$CHCl_3$	–20	85	84 (*R*)
8	**107e**, 2-Naphth, Me	(*S*)-**124** (10)	$CHCl_3$	–20	93	94 (*R*)
9	**107a**	(*S*)-**113c** (10)	Toluene	–20	94	81 (*R*)
10	**107f**, *c*-C_6H_{11}, Me	(*S*)-**113c** (10)	Toluene	–20	90	88 (*R*)

different type of Lewis-basic activator, built around a (pyridyl)oxazoline [105, 106] framework, such as **123** and **124**, derived from mandelic acid. The remote position of the stereogenic center turned out to be vital for catalyst performance as the positional isomer of **123** derived from phenylglycinol, where the phenyl substituent is adjacent to the carbon next to the nitrogen atom, was significantly less efficient in terms of reactivity and enantioselectivity. Importantly, catalysts **123** and **124** proved to be equally efficient in the reduction of aromatic ketimines **106** and ketones **107** (Table 15.8, entries 17, 18 and Table 15.10, entries 6–8), which places them among the rare systems (including metal catalysts [107]) applicable to both imines and ketones. Later, Sun [98e] introduced catalyst **113c**, which also possessed the same ability (Table 15.10, entries 9, 10).

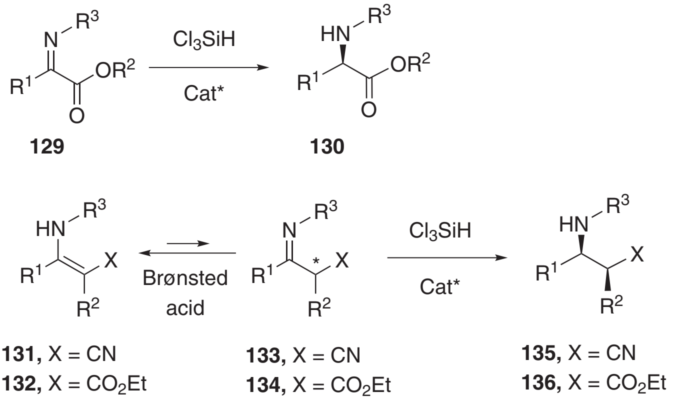
After the methodology for asymmetric reduction of imines with trichlorosilane employing model substrates had been firmly established, the focus of research in the field gradually shifted towards the synthesis of functionalized chiral amines, which represent important building blocks for pharmaceutical, agricultural, and fine chemical industries.

Malkov and Kočovský [97c] reported that the readily available α-chloroacetophenones **125** can be converted into the corresponding α-chloro-imines **126**, whose reduction with Cl_3SiH, catalyzed by Sigamide **114b** (5 mol%), afforded vicinal chloroamines (*R*)-**127** in >90% ee (Scheme 15.26). The subsequent base-catalyzed ring closure of the resulting amino chlorides **127** produced the corresponding aziridines **128** with retention of the stereochemical integrity. Pertinently, in many instances the isolation of α-chloro imines proved cumbersome to the extent that the subsequent reduction could not be carried out. Therefore, a direct reductive amination protocol was developed, where the chloro-imines **126** were generated *in situ* (toluene, 5 Å MS, room temperature) and, without isolation, treated with trichlorosilane. Later, Benaglia [102d] and Jones [103b] extended the reductive amination technique to a range of other ketones.



Scheme 15.26

Reduction of α-imino esters **129** to afford α-amino acid derivatives **130** (Scheme 15.27) proceeded in good yields but in the case of catalysts **114a** [97b, 97e], **117a** [101], **118a** [102a], and **120a** [102b] the enantioselectivities were lower than expected (Table 15.11, entries 1–3, and 5). However, replacing the proline core in **118a** with 4-hydroxyproline, as in **118b**, led to a substantial increase in selectivity (compare entries 3 and 4) [102e].



Scheme 15.27

Table 15.11 Asymmetric synthesis of α-amino acid derivatives (Scheme 15.27 and Figures 15.5 and 15.6).

Entry	Imine R^1, R^2, R^3	Catalyst (mol%)	Solvent	Temperature (°C)	Yield (%)	ee (%) (config.)
1	**129a**, Ph, Me, Ph	(*S*)-**114a** (10)	Toluene	–20	69	59 (*R*)
2	**129a**	(*S*)-**117a** (10)	CH_2Cl_2	0	99	81 (*S*)
3	**129a**	(*S*)-**118a** (10)	CH_2Cl_2	Ambient	80	45 (*R*)
4	**129b**, Ph, Et, *p*-methoxyphenyl (PMP)	(*S,R*)-**118b** (10)	CH_2Cl_2	–20	98	90 (*R*)
5	**129b**	(*S,R*)-**120a** (10)	$CHCl_3$	–20	85	65 (*R*)

Next to be investigated were the members of the homologous series, namely, β-imino nitriles **133** and β-imino esters **134**, existing predominantly in the conjugated enamine forms **131** and **132**, which cannot be reduced with trichlorosilane (Scheme 15.27) [97d]. However, Malkov and Kočovský found that Brønsted acids can facilitate the enamine–imine equilibrium and provide sufficient concentration of the desired imine form, whose reduction can now be accomplished. In the case of Sigamide **114b**, acetic acid (1 equiv) was identified as an optimal additive: the reduction, carried out in its presence, afforded the expected β-amino nitriles **135** and β-amino esters **136** in high yields and enantioselectivities (Table 15.12, entries 1 and 2).

A slightly modified approach was reported by Sun [100d] for the reduction of *N*-benzyl derivative **132d** using catalyst **116b**. The requisite Brønsted acid, in this

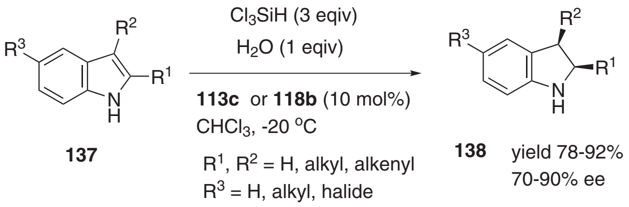
Table 15.12 Asymmetric synthesis of β-amino acid derivatives (Scheme 15.27 and Figures 15.5 and 15.6).

Entry	Enamine R^1, R^2, R^3	Catalyst (mol%)	Solvent	Temperature (°C)	Yield (%)	d.r.	ee (%)
1	**131a**, Ph, H, PMP	**114b** (5)	Toluene	Ambient	75	–	87
2	**132a**, Ph, H, PMP	**114b** (5)	Toluene	Ambient	98		89
3	**131b**, Ph, Ph, PMP	**114b** (10)	Toluene	Ambient	46	99 : 1	83
4	**132b**, Ph, Ph, PMP	**114b** (10)	Toluene	Ambient	84	99 : 1	76
5	**132c**, Ph, Et, PMP	**114b** (10)	Toluene	Ambient	86	95 : 5	82
6	**132d**, Ph, H, Bn	**116b** (5)	Toluene	–40	98	–	96
7	**132d**	**117b** (5)	CH_2Cl_2	–40	50	–	85
8	**132e**, Ph, H, H	**118a** (10)	CH_2Cl_2	Ambient	65		41
9	**132f**, Ph, OAc, PMP	**119** (10)	1,2-Dichloroethane (DCE)	–10	95	91 : 9	94

case HCl, was generated by adding 1 equiv of H_2O to the reaction mixture containing a threefold excess of Cl_3SiH. Excellent yield and enantioselectivity were attained (Table 15.12, entry 6). Traces of HCl present in the commercial Cl_3SiH were found to be sufficient to accomplish reduction of **132d** using catalyst **117b** (85% ee, entry 7) [101]. Notably, the method can be used for the synthesis of unprotected β-phenylalanine ester **136e**, though in modest enantioselectivity (entry 8) [102a].

This strategy has been extended by Malkov and Kočovský to the reduction of imines/enamines derived from α-substituted β-keto nitriles and β-keto esters (Scheme 15.27, **131**–**134**, $R^2 \neq H$) [97d]. In this case, the fast enamine–imine equilibration plays a crucial role, since imines **133** and **134** are chiral but racemic, so that dynamic kinetic resolution is required here along with the enantioselective reduction to provide good diastereo- and enantiocontrol. The α-aryl derivatives **135b** and **136b**, for which no other suitable methodology is available, were obtained as single diastereoisomers in good yields and respectable enantioselectivities (Table 15.12, entries 3 and 4). Reduction of α-alkyl derivative **132c** followed the same pattern (entry 5). The method has been shown by Zhang to be applicable to the synthesis of α-hydroxy β-amino acid derivatives [102h]: enamide **132f** was thus reduced in the presence of catalyst **119** in good diastereoselectivity (91 : 9) and high ee (93% ee, entry 9).

Recently, the methodology was successfully employed for the enantioselective reduction of indoles **137** into indolines **138** using catalysts **113c** and **118b** (Scheme 15.28) [98g]. To facilitate the enamine/imine tautomeric equilibrium, the required Brønsted acid was generated by a controlled hydrolysis of excess trichlorosilane with water.

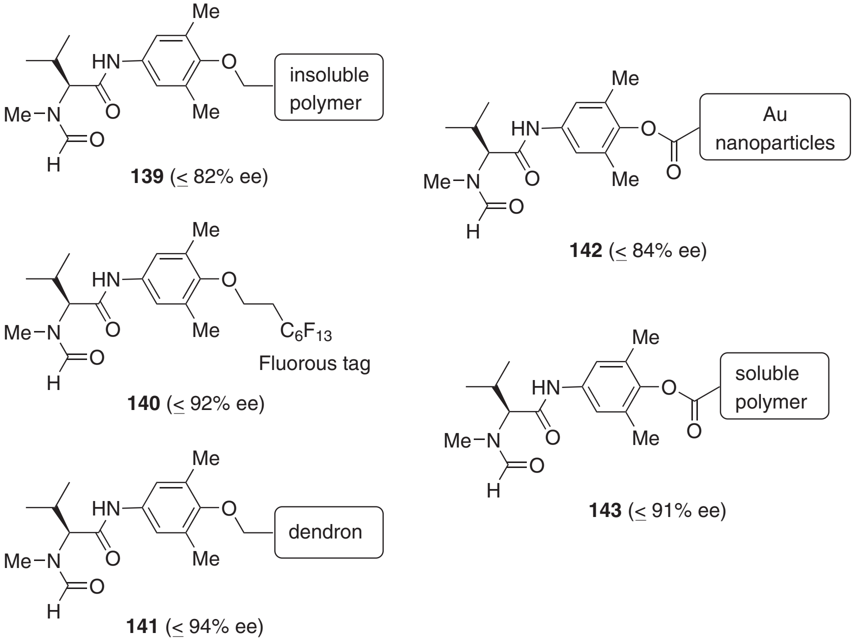


137

138

Scheme 15.28

The formamide-type catalysts **114**, developed by Malkov and Kočovský (Figure 15.5) [97], proved to be very efficient and, as a result, the loading could be reduced to 1–5 mol% (Tables 15.8, and 15.11). Nevertheless, even this relatively small amount still appears as a contaminant in the product and has to be separated. Therefore, several strategies for immobilizing the catalysts have been investigated (Figure 15.7). The most convenient of them from a practical point of view is to anchor the catalyst to a traditional solid polymer support, such as Merrifield, extended Merrifield, Wang, TentaGel, and Marshall resins (**139**) [108]. After completion, simple filtration separated the catalyst from the reaction mixture. However, the heterogeneous nature of the catalysis led to a noticeable drop in enantioselectivity (≤82% ee). Appending the catalysts to a fluorous tag **(140)** [109] or a third-generation dendron (**141**) [110] kept the reaction homogeneous, which allowed retention of the selectivity exhibited by the untagged counterpart. The catalyst with



139 (≤ 82% ee)

142 (≤ 84% ee)

140 (≤ 92% ee)

143 (≤ 91% ee)

141 (≤ 94% ee)

Figure 15.7 Various strategies employed for the immobilization of catalysts.

a fluorous tail (**140**) was recovered by filtration through a pad of fluorous silica, whereas **141** was removed by precipitation with methanol, followed by centrifugation. Notably, though, these two strategies require rather costly materials for their synthesis and operation. Immobilization of the catalysts on gold nanoparticles (**142**) was also accomplished [111], but lower enantioselectivity was observed, which was aggravated by a further drop in activity of the recovered catalysts.

The best practical solution has been achieved by anchoring catalyst **114** to a soluble poly(methacrylate) backbone (**143**) [112]. In this instance, the reactions proceeded under homogeneous conditions at room temperature in toluene and the catalyst was recovered almost quantitatively and re-used at least five times without loss of activity. A wide range of chiral amines **108** were obtained in high yields and with good enantioselectivity (≤91% ee) at 1–7 mol% catalyst loading [112].

Trialkoxysilanes are less sensitive to moisture and thus represent an attractive alternative to trichlorosilane as reducing reagents. However, activation of trialkoxysilanes requires stronger bases, such as alkoxide-anions, and this area remains in the early stages of development. Hosomi [113] investigated a catalytic reduction of tosylimine **106** (R^1 = Ph, R^2 = Me, R^3 = Ts) with $(MeO)_3SiH$, screening several chiral alcoholates. The dilithium salt of BINOL (20 mol%) emerged as the best, producing the corresponding tosylamide **108** in 65% ee. However, attempts to improve the catalyst structure have proved fruitless to date.

An alternative method for organocatalytic reduction of imines employs Brønsted acids as catalysts and Hantzsch dihydropyridine as a reducing reagent. This topic is dealt with in the chapter on Brønsted acids (Chapter 11) [114].

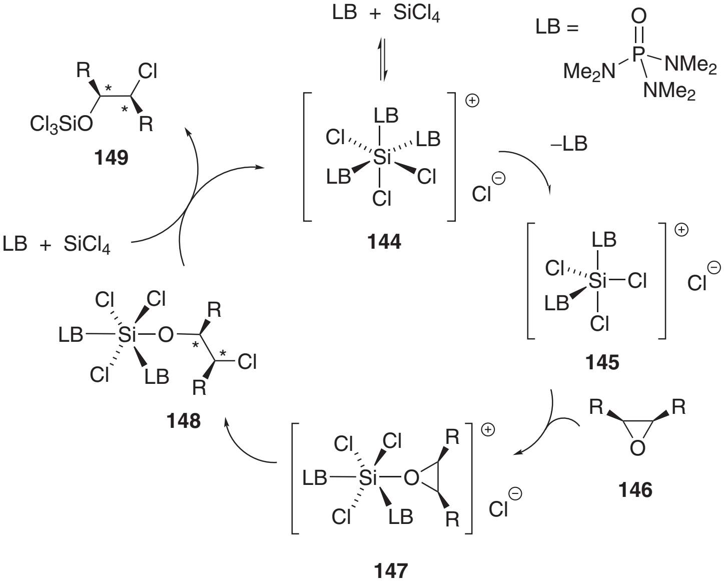
Typical Procedure for the Catalytic Hydrosilylation of Imines [109]

Trichlorosilane (40 μl, 0.4 mmol) was added dropwise to a stirred solution of the imine **106b** (45 mg, 0.2 mmol) and catalyst **114b** (3.5 mg, 0.01 mmol) in anhydrous toluene (2 ml) at 0 °C, and the mixture was allowed to stir overnight at room temperature under an argon atmosphere. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 ml) and the product was extracted with ethyl acetate (3 × 30 ml). The extract was washed with brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated. Purification using column chromatography on silica gel with a hexane–ethyl acetate mixture (10 : 1, R_f 0.3) afforded amine (*S*)-(−)-**108b** (43 mg, 95%) as an oil: $[\alpha]_D$ −4.0 (*c* 1.0, $CHCl_3$); chiral HPLC (Chiracel OD-H, hexane/2-propanol, 99 : 1, 0.9 ml min^{-1}) showed 94% ee (t_R = 21.6 min, t_S = 24.4 min).

15.7
Epoxide Opening

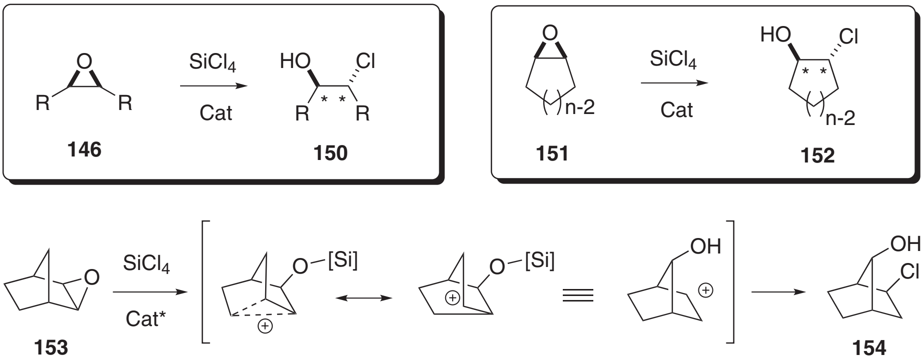
Epoxides are versatile intermediates in organic synthesis owing to their potential for stereospecific ring opening. The ability of various chlorosilanes to serve as a source of chloride ion for the opening of epoxides was recognized over half a century ago [115]. Later, it was demonstrated that the reaction can be dramatically accelerated by nucleophilic catalysts, such as phosphines, imidazole [116], and, most recently, by phosphorous heterocycles [117] and HMPA [118].

The mechanism of the nucleophile-assisted opening of epoxides has been thoroughly investigated by Denmark (Scheme 15.29), who used a rapid injection NMR technique [119]. HMPA was employed as a Lewis base (LB). Initially, the monodentate LB and tetrachlorosilane form the 3 : 1 cationic hexacoordinate complex **144**, which is the resting state of the catalyst. Dissociation of LB gives rise to the coordinatively unsaturated species **145**, which can interact with epoxide **146** to form complex **147**. Opening of the activated epoxide by chloride ion may proceed either in an S_N2 or S_N1 fashion, depending on the structure of the epoxide, to give intermediate **148**. Owing to the reversible nature of the donor–acceptor interactions between the Lewis base and silicon, complex **144** is then regenerated, releasing the resulting chlorohydrin **149**, which completes the catalytic cycle.



Scheme 15.29

According to this mechanism (Scheme 15.29), the process is amendable to asymmetric modifications. Among various silicon reagents that were examined, only tetrachlorosilane proved to be suitable for the asymmetric process, while application of other chlorosilanes resulted in the formation of racemic products. Several chiral Lewis bases were investigated in the opening of *meso*-epoxides **146** and **151** (Scheme 15.30) to produce the corresponding chlorohydrins **150** and **152**, respectively. Opening of the norbornene-derived epoxide **153** was found to proceed



Scheme 15.30

with a rearrangement, giving rise to chloroalcohol **154** [120]. The most successful catalysts **19**, **26**, **30**, **82**, and **155–158** are shown in Figure 15.8 with a selection of representative examples highlighted in Table 15.13.

In general, the efficiency of the catalysts was found to be substrate dependent; none of the catalysts was able to provide a good level of enantioselectivity with a wide range of acyclic (**146**) and cyclic (**151**) epoxides (Scheme 15.30). Bis-isoquinoline *N*,*N*′-dioxides **26** [121] and **82** [122], BINAPO **30** [123], the axially chiral phosphoramide **155** [118], axially chiral allene-derived phosphine oxide **156** [124], planar chiral pyridine *N*-oxide **157** [125], and helical chiral pyridine *N*-oxide **158** [126] exhibited high enantioselectivity in the opening of derivatives of *cis*-stilbene oxide **146a** (R = Ar) (Table 15.13, entries 1–7). In the case of the less sterically demanding aliphatic **146b** (R = CH_2OBn) and cyclic epoxides **151a**, the

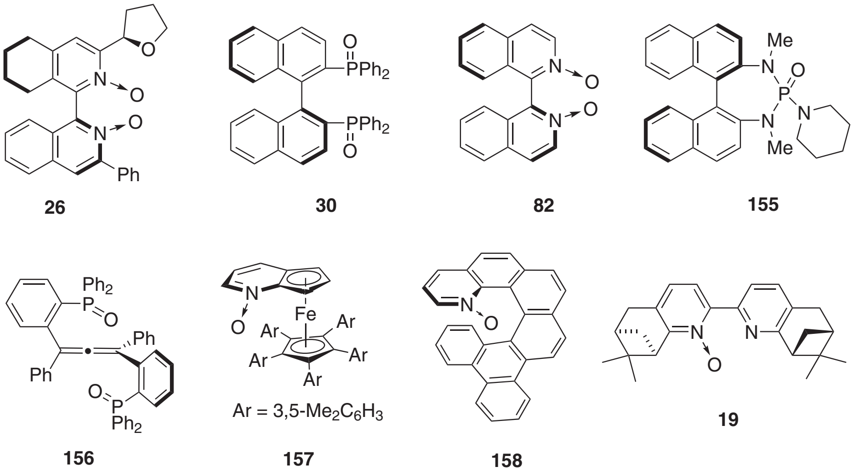


Figure 15.8 The most successful catalysts in epoxide opening.

Table 15.13 Enantioselective ring opening of *meso*-epoxides catalyzed by chiral Lewis bases (Scheme 15.30 and Figure 15.8).

Entry	Epoxide	Catalyst (mol%)	Time (h)	Temperature (°C)	Yield (%)	ee (%)
1	**146a**, R = Ph	**26** (5)	1	–40	74	64
2	**146a**	**30** (10)	4	–78	94	90
3	**146a**	**82** (10)	6	–78	95	90
4	**146a**	**155** (10)	3	–78	94	87
5	**146a**	**156** (0.1)	12	–78	97	94
6	**146a**	**157** (5)	24	–85	88	94
7	**146a**	**158** (10)	48	–78	77	94
8	**146b**, R = CH_2OBn	**82** (10)	6	–78	98	74
9	**146b**	**155** (10)	4	–78	95	71
10	**146b**	**156** (0.2)	36	–78	90	60
11	**146b**	**157** (5)	24	–85	91	50
12	**146b**	**158** (10)	48	–78	72	65
13	**151a**, $n = 6$	**26** (5)	5	–78	30	53
14	**151a**	**30** (10)	1	–78	81	71
15	**151a**	**155** (10)	0.3	–78	90	51
16	**151b**, $n = 8$	**19** (10)	48	–90	93	90
17	**151c**, $n = 12$	**19** (10)	48	–90	67	84
18	**153**	**19** (10)	48	–90	53	90

selectivity with these catalysts dropped to a moderate level and below (entries 8–15). Cyclooctene oxide **151b** ($n = 8$) proved to be a particularly difficult substrate, displaying low reactivity and selectivity with most of the Lewis bases except for the pyridine mono-*N*-oxide **19** [27a, 120], which furnished the corresponding chlorohydrin in 90% ee (entry 16). Catalyst **19** was also active with other cyclic epoxides, namely, **151c** and **153** (entries 17, 18). The latter example is worth special attention since formation of **154** (Scheme 15.30) proceeded by Wagner–Meerwein rearrangement, suggesting that the S_N1 mechanistic manifold operates predominantly in this case with a high degree of ionization of the C–O bond in the initially formed complex of the epoxide with Si species. On the other hand, unlike all the other catalysts, **19** was ineffective with non-cyclic substrates [120].

Typical Procedure for the Catalytic Desymmetrization of *meso*-Epoxides [120]

Tetrachlorosilane (86 μl, 0.75 mmol) was added dropwise to a stirred solution of cyclooctene oxide **151b** (100 mg, 0.51 mmol) and catalyst **19** (18.0 mg, 0.05 mmol) in anhydrous dichloromethane (5 ml) at –90 °C. After stirring for 48 h the reaction mixture was quenched with a saturated aqueous solution of KF and K_2HPO_4 (1 : 1, 5 ml) and the organic phase was diluted with diethyl ether (10 ml). The organic layer was then separated and the aqueous layer was extracted with diethyl ether (3 × 15 ml). The combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography on silica gel with petroleum ether–ethyl acetate (10 : 1) afforded (−)-**152b** (74 mg, 91%) as a colorless solid, mp 49–50 °C; $[\alpha]_D$ −26.4 (*c* 1.0, $CHCl_3$); ^{19}F NMR of the corresponding Mosher ester derivative showed 90% ee [δ −71.32 (95.0%), −71.86 (5.0%)].

15.8
Conclusion and Outlook

Organocatalysis, in general, is experiencing a fascinating boom, and Lewis-basic catalysts are no exception. The chemistry covered in this chapter is dominated by silicon, an inexpensive and environmentally friendly element. Hence, at the top of the fundamental issues being addressed by this research, significant practical applications can be expected in the near future. Further development of the catalytic, enantioselective processes discussed in this chapter will undoubtedly continue, aimed at more efficient catalysts, lower catalyst loading, and simplification of their synthesis, and so on, all supported by detailed mechanistic studies. Clearly, more valuable methodology and new concepts involving Lewis bases as catalysts are on the horizon.

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16

Lewis Acids

Tatjana Heckel and René Wilhelm

16.1

Introduction

For several decades the term asymmetric catalysis was nearly a synonym for the application of metal complexes with chiral ligands. Thanks to the use of different metals, ligands, and oxidation states it is possible to tune selectivity and asymmetric induction very easily. Hence, this approach to asymmetric catalysis was nearly the only recognized one in the last three decades of the twentieth century [1, 2]. In many examples the metal is a Lewis acid [3].

However, many properties that are normally associated with metals as Lewis acids and as redox agents [4, 5] can be also emulated by organic compounds [6]. This chapter introduces the reader to the research field of Lewis acid organocatalysts. Compared to other types of organocatalysts, which are highlighted in other chapters of this book, the field of Lewis acids consists of a limited number of examples. The number of asymmetric versions of these types of catalysts is even more limited and the obtained enantiomeric excesses are often low. Hence, this chapter will also discuss a few examples that are catalyzed by achiral organic Lewis acids. Therefore, we will also cover several reactions promoted by achiral catalysts. Taking into consideration the broad variety of possible reactions that can be catalyzed by Lewis acids it is highly desirable to develop this research field further.

Carbenium, silyl, or phosphonium cations are active Lewis acids. In addition, hypervalent phosphorus and silicon compounds can act as Lewis acids. Furthermore, ionic liquids, which are organic salts with a melting point below 100 °C, can act as Lewis acids. They can catalyze reactions either in substoichiometric amounts or, if used as the reaction medium, in stoichiometric or even larger quantities. The solvents can be efficiently recovered after the reaction.

This chapter will concentrate on metal-free Lewis acids that possess a Lewis acidic cation or a hypervalent center. Lewis acids are compounds with a vacant orbital [7, 8]. It is also possible to consider two successful classes of organocatalysts as part of Lewis acids catalysts. Chiral Brønsted acid organocatalysts could be considered due to their proton, which is the simplest Lewis acid. The achieved

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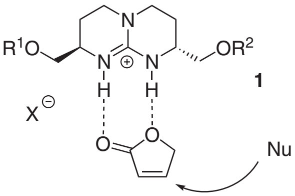


1

Figure 16.1 Chiral guanidinium salt **1**, an example of an organocatalyst that works by hydrogen bond activation.

enantioselectivities are due to the formation of a chiral ion pair. The other class is hydrogen bond activating organocatalysts, which can be considered to be Lewis acids or pseudo-Lewis acids. These two types will be discussed in different chapters of this book and are a separate class of organocatalyst.

As indicated above, many organocatalytic Lewis acids consist of organic cations. Yet not all organic cations can be considered to be Lewis acid organocatalysts although they are being applied as organocatalysts. Chiral guanidinium salt **1**, for example, catalyzes a Michael reaction [9]. As can be seen in Figure 16.1 this salt belongs to the hydrogen bond activating organocatalysts due to the mode of activation. In the presented example, **1** gave only racemic product (Figure 16.1). A chiral amidinium salt [10], which catalyzed the Diels–Alder reaction with significant enantiomeric excess, also belongs to the class of hydrogen bond activating organocatalysts.

Ammonium cations of the types RNH_3^+, $R_2NH_2^+$, or R_3NH^+ belong to the class of Brønsted acids or hydrogen bond activating organocatalysts as well. In addition, tetra-substituted ammonium cations, R_4N^+, could interact slightly with, for example, a carbonyl group, lowering the electron density of its carbon atom. However, the ammonium cation is not a Lewis acid because it is lacking an empty orbital to take up an electron pair. Nonetheless, enantiopure quaternary ammonium salts are very efficient in asymmetric phase-transfer catalysis, and have been reviewed [11–20].

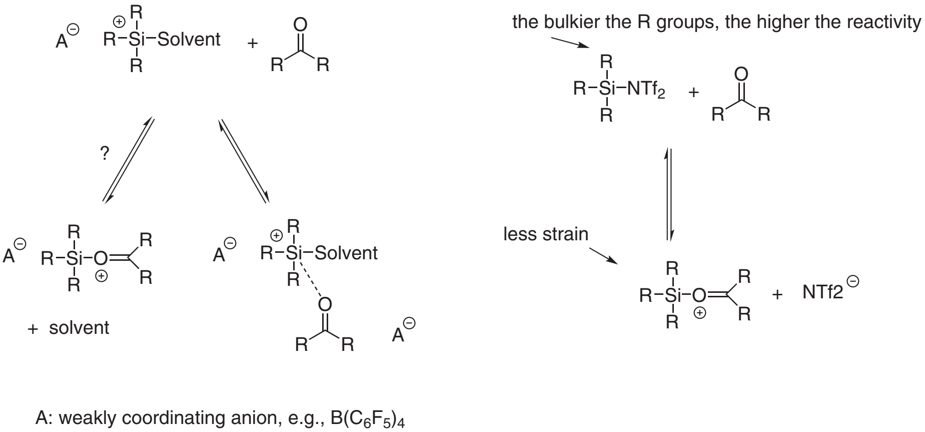
This chapter will give first an overview of silyl cations. Thereafter, very briefly, hypervalent silicon compounds will be discussed. Strictly speaking, the concept of hypervalent silicon compounds is part of Lewis base catalysis and will be discussed there in detail. However, since in this type of reaction a Lewis base forms *in situ* with a silicon atom containing reagent or $SiCl_4$ an intermediate, which functions as a Lewis acid to activate substrates during the reaction, we also give here a few examples. Notably, silicon is a semimetal. Hence, we leave it up to the reader to decide whether silicon catalysts should be considered as organocatalysts.

The semimetal boron has long been used as a Lewis acid, for example, BF_3, and enantiopure derivatives have been applied in many reactions very successfully. Asymmetric boron catalysts have been reviewed [21–24] and are not included in this chapter.

16.2
Silyl Cation Based Catalysts

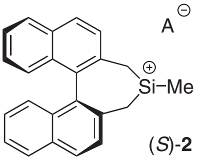
Silicon cation based Lewis acids have been reported in the literature for a long time and their application in catalysis has been reviewed [25]. Most examples in the literature are based mainly on achiral species and will be presented in this section only briefly. A broad variety of reactions can be catalyzed with compounds like Me_3SiOTf, Me_3SiNTf_2, or Me_3SiClO_4. These Lewis acids are compatible with many carbon nucleophiles such as silyl enol ethers, allyl organometallic reagents, and cuprates.

Scheme 16.1 shows the two possible modes of activation of silyl Lewis acids. The different Lewis acidic species depend on how strong the counter anion interacts with the silicon atom. In the first case, if the counter anion is a very weakly coordinating one, it is possible to consider that a free silyl cation is present. In this case the silyl cation will be coordinated by solvent molecules, such as acetonitrile or toluene, due to the Lewis acidic strength of the silyl cation [26, 27]. This solvent coordinated silyl cation could then, for example, activate a carbonyl group. It has not been determined yet if the carbonyl group replaces the solvent molecule. In the second case, if a more coordinating anion is present, a neutral silicon molecule can be postulated. During the activation of a carbonyl group an exchange with the $[NTf_2]$ ligand would occur. Replacement of the large $[NTf_2]$ substituent with a smaller carbonyl ligand would be faster the bulkier the three alkyl groups around the silicon atom are, due to the release of strain [28–30].


A⊖ R–Si⊕(R)(R)–Solvent + RC(O)R
?
A⊖ R3Si–O⊕=CR2
+ solvent
A⊖ R3Si⊕–Solvent ··· O=CR2 A⊖
A: weakly coordinating anion, e.g., $B(C_6F_5)_4$
the bulkier the R groups, the higher the reactivity
R3Si–NTf2 + RC(O)R
less strain
R3Si–O⊕=CR2 + NTf2⊖

Scheme 16.1

The groups of Jørgensen and Helmchen reported in 1998 the synthesis of the chiral silyl cationic salt **2** (Figure 16.2) [31]. This was the first enantiopure silyl cation used as a catalyst in an asymmetric reaction. To ensure that the silyl salt had a high reactivity, the almost chemically inert and non-coordinating anions



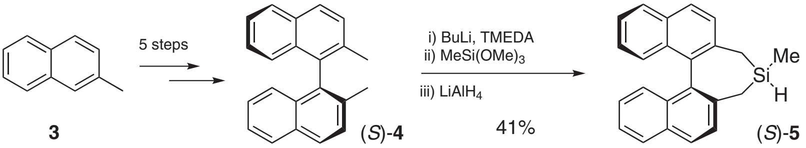
(*S*)-**2**

a A = TPFPB
b A = TFPB

Figure 16.2 First enantiopure silyl cation used as a catalyst in an asymmetric reaction.

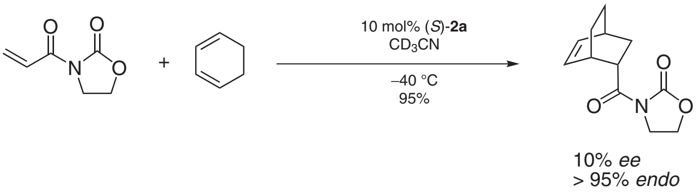
tetrakis[pentafluorophenyl]borate (TPFPB) and tetrakis[3,5-bis(trifluoromethyl) phenyl]borate (TFPB) were chosen as counter anions.

To prepare salt **2** compound **5** was first prepared according to Scheme 16.2. Binaphthyl compound (*S*)-**4** was prepared from 2-methylnaphthalene (**3**) over five steps. Owing to a resolution step the compound was obtained enantiopure [32–34]. In the last step precursor (*S*)-**5** was synthesized in 41% yield as shown in Scheme 16.2.



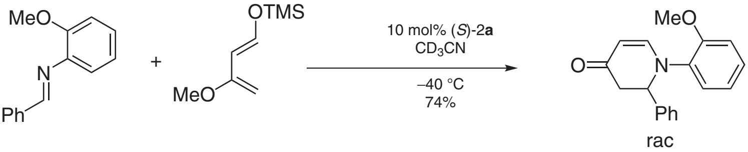
Scheme 16.2

The salts (*S*)-**2a** and (*S*)-**2b** are highly reactive and moisture sensitive. Therefore, they were prepared *in situ* from the air and moisture stable precursor (*S*)-**5** via a hydride transfer [35, 36] with trityl TFPB ([Tr][TFPB]) or trityl TPFPB ([Tr][TPFPB]). ^{29}Si-spectra revealed that the desired salts were formed. Salt (*S*)-**2a** was then used as a catalyst in the Diels–Alder reaction shown in Scheme 16.3. The product was obtained at −40 °C in 1 h with an excellent yield of 95%. The endo selectivity was 95%. Unfortunately, only a low ee of 10% was found.



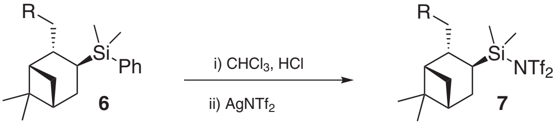
Scheme 16.3

Salt (*S*)-**2a** was also able to catalyze the aza-Diels–Alder reaction as presented in Scheme 16.4. Benzylidene-2-methoxyaniline and Danishefsky's diene gave with the catalyst the product in 74% yield with 10 mol% catalyst at –40 °C in 2 h. The product was racemic.



Scheme 16.4

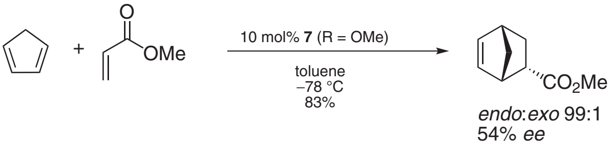
Another enantiopure silicon-based catalyst was reported by the group of Ghosez [28]. They took the results of Simchen and Jonas [29] as described above into consideration, namely, that R_3SiNTf_2 compounds with bulky chiral groups should have a high catalytic activity. Silylated sulfonimides were synthesized from readily available (–) myrtenal over a few steps, resulting in the precursors **6** shown in Scheme 16.5. The desired salts were obtained *in situ* from silane **6** by preparing the corresponding silyl chloride, made from **6** and HCl in $CHCl_3$, and then treating it with $AgNTf_2$.



R = Et 67%
R =OMe 71%
R = OCH_2Ph 86%
R = OCOPh 30%

Scheme 16.5

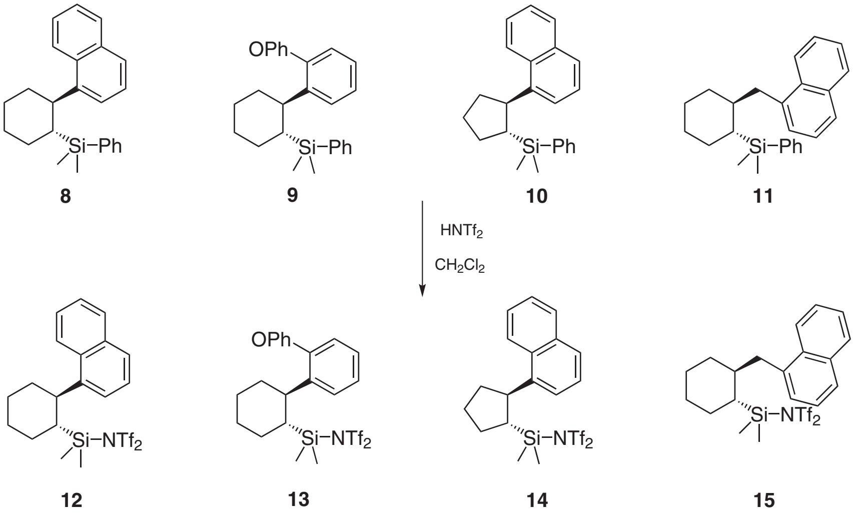
Compounds **7** were explored in the Diels–Alder reaction of cyclopentadiene and methyl acrylate. The best result is shown in Scheme 16.6. Compound **7** (R = OMe) with an oxygen atom that stabilizes the silicon atom through coordination, gave the desired product in 83% yield with an ee of 54%. The *endo* product was



Scheme 16.6

obtained as the major product in 1.5 h. When **7** (R = Et) had no oxygen atom a significantly lower ee of 7% was found. Beside toluene, other solvents such as ether, propionitrile, or CH_2Cl_2 were explored in the reaction; however, no product was formed.

In addition, enantiopure cycloalkylsilyl triflimides were also prepared by the same group [37]. They are depicted in Scheme 16.7. The corresponding precursors were synthesized from cyclohexenones and cyclopentanones. They were transferred in three steps into racemic 2-aryl- and arylmethyl-3-dialkylphenylsilyl cycloalkanones. The resulting racemic compounds were resolved by preparative chiral HPLC. Thereafter, the carbonyl function was removed to furnish the precursors to the silyl triflimides. The latter were formed *in situ* directly by treatment with $HNTf_2$. Formation of the silyl triflimides was observed by ^1H NMR through the peaks of the methyl groups next to the silicon atom. The signals shifted from 0.20 to 0.60 ppm. Furthermore, a peak at 7.36 ppm appeared due to the benzene released during the reaction.



Scheme 16.7

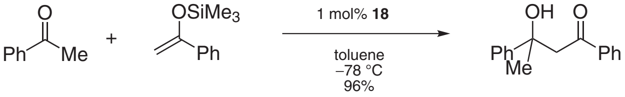
Compounds **12–15** were then applied as catalysts in the Diels–Alder reaction of methyl acrylate and cyclopentadiene (Scheme 16.6). Compared to the previous study [28], CH_2Cl_2 was the best solvent for the reactions. The catalyst was formed *in situ*, and the reaction was carried out at −78 °C with 2,6-di-*tert*-butyl-4-methylpyridine to trap residual $HNTf_2$. The best result gave compound **12** and the product was isolated in high *endo* selectivity in 96% yield and 50% ee. At a reaction temperature of −100 °C a yield of 94% and an ee of 59% was reached in less than 2 h. In contrast to the previous example catalyst **13**, containing an oxygen atom, gave low *endo* selectivity and a low ee of 35%. The cyclopentane based analog **14** resulted in an ee of 56%. The *endo/exo* selectivity was only 32%. In case of catalyst **15**, with a methylene group inserted between the cyclohexene ring and the 1-naphthyl group, a significantly lower ee of 7% was found due to the higher conformational mobility in this catalyst.

The influence of different counter anions on the catalytic activity of cationic silicon Lewis acids was explored by Sawamura *et al.* [38]. In their studies an achiral salt was investigated. In previous studies [31] acetonitrile was used as a solvent. However, this is known to strongly coordinate silicon cation species. Therefore, toluene was used as a solvent in the investigation of silicon cationic species. Despite the fact that toluene can also coordinate a silicon cation [26, 39], an enhanced activity compared to other solvents was observed. The achiral salt was formed *in situ* from triethylsilane and $[Ph_3C][B(C_6F_5)_4]$ (**17**) (Scheme 16.8).

$$\underset{\mathbf{16}}{Et_3SiH} + \underset{\mathbf{17}}{[Ph_3C][B(C_6F_5)_4]} \xrightarrow[\text{toluene}]{} \underset{\mathbf{18}}{[Et_3Si(\text{toluene})][B(C_6F_5)_4]} + \underset{\mathbf{19}}{Ph_3CH}$$

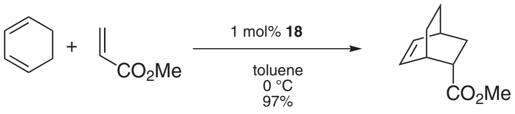
Scheme 16.8

The salt **18** was used as a catalyst in the Mukaiyama aldol reaction with acetophenone. A yield of 96% was obtained after 1 h at −78 °C (Scheme 16.9). With the simple catalyst Me_3SiOTf no product was formed. Me_3SiNTf_2 and Et_3SiNTf_2 gave low yields of 12% and 8%, respectively.



Scheme 16.9

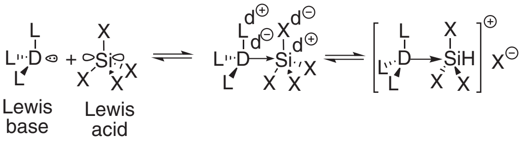
Furthermore, it was found that salt **18** could catalyze the Diels–Alder reaction and the *endo*-product was obtained in 97% yield after 1 h (Scheme 16.10). Again, Me_3SiOTf showed no catalytic activity, while Me_3SiNTf_2 and Et_3SiNTf_2 gave a yield of 6% and 13%, respectively. Both reactions with salt **18** were also carried out in the presence of the proton scavenger 2,6-di-*tert*-butylpyridine. The same results were obtained, which ruled out a proton-promoted reaction.



Scheme 16.10

16.3
Hypervalent Silicon Based Catalysts

Silicon-containing reagents can form *in situ* with Lewis bases a Lewis acid center, which can activate a substrate. However, this type of reaction belongs more to the field of Lewis base organocatalysis. Therefore, very few examples will be discussed here. Taking the valence shell expansion capability of silicon into consideration, Lewis bases can interact with vacant orbitals residing on the silicon. This interaction increases the electron density on the most labile ligand of the silicon atom. This ionizes or partially ionizes the labile ligand and a positively charged silicon complex is formed. The later can act as a Lewis acid due to its free 3d-orbitals, which are responsible for many organic transformations (Scheme 16.11) [25, 40–45].

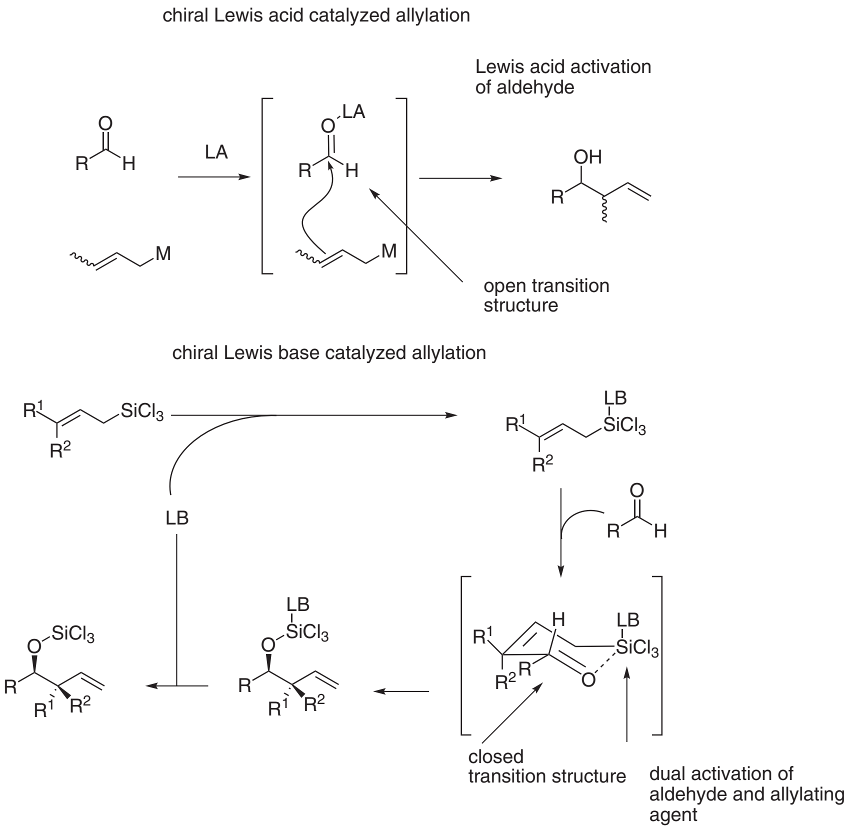


Scheme 16.11

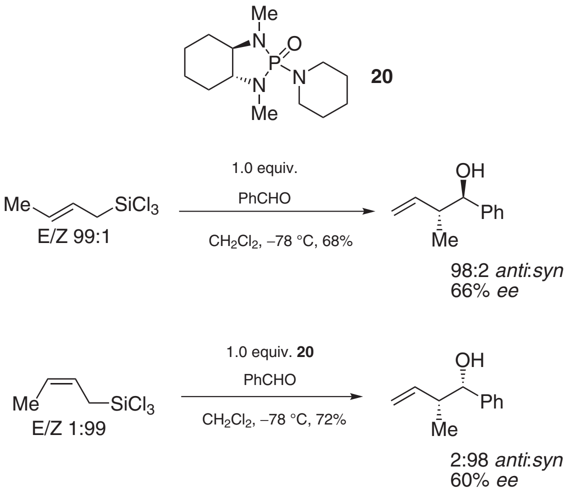
Here, an example with a silicon atom in one of the reaction partners will be presented. The asymmetric allylation of carbonyl compounds gives homoallylic alcohols with two consecutive stereocenters during the carbon–carbon bond formation. Prior to the application of silyl-containing allylation reagents with Lewis bases, Lewis acids that activate an electrophilic aldehyde towards nucleophilic attack of an allyl metal reagent were used (Scheme 16.12) [2]. The later method gives high enantioselectivity, but low to no diastereoselectivity, because of the non-rigid transition state in the reaction. In Lewis base catalyzed allylations a dual mechanism of activation is present, which includes the Lewis base and a nucleophilic trichlorosilane species. This way a reactive hypercoordinated silicate species is created, which further coordinates with aldehydes. Because the reactions proceed in the close assembly of a six-membered ring transition state with allyltrichlorosilane, aldehyde, and chiral Lewis base, a high degree of diastereoselectivity and enantioselectivity can be obtained [41].

The first example of an enantiopure Lewis base promoted allylation was reported by Denmark and coworkers in 1994 [46]. Stoichiometric amounts of the enantiopure phosphoramide (*R,R*)-**20** promoted the enantioselective allylation (Scheme 16.13). There was a complete stereochemical correlation between the geometry (*E*/*Z*) of allylsilane and the diastereomeric ratio (*syn*/*anti*) of the products.

Because the reaction type mentioned above belongs more to the field of Lewis base catalyzed reaction, we will now focus on enantiopure silicon allylation reagents that already incorporate Lewis acidity. The Lewis acidity of tetravalent silicon


chiral Lewis acid catalyzed allylation
Lewis acid activation of aldehyde
LA
open transition structure
chiral Lewis base catalyzed allylation
LB
closed transition structure
dual activation of aldehyde and allylating agent

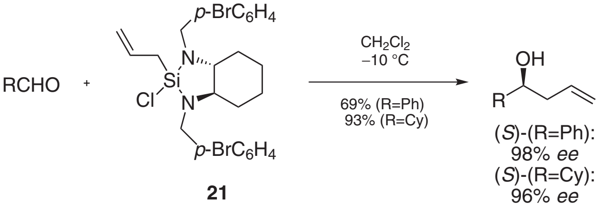
Scheme 16.12



Scheme 16.13

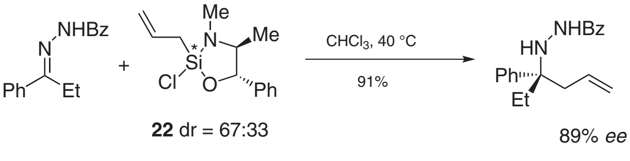
and its high tendency to expand its valence shell increases [47, 48] when incorporated into strained four- or five-membered ring systems (strain-release Lewis acidity) [49]. This is due to smaller energy gaps between sp [3] and dsp [3] orbitals of a strained system as compared to an acyclic species.

Leighton *et al.* have applied this concept of strained silacycles [50–54] for the asymmetric allylation in a series of publications [48, 55–57]. Leighton's allylic silacyclopentane **21** [55] (Scheme 16.14) allows the allylation of aromatic and aliphatic aldehydes in the absence of additional Lewis bases (promoter activator) or Lewis acids with high yield and enantioselectivity. The reaction proceeds probably over a cyclic transition state with a trigonal bipyramidal geometry at a pentacoordinated silicon [47, 58].



Scheme 16.14

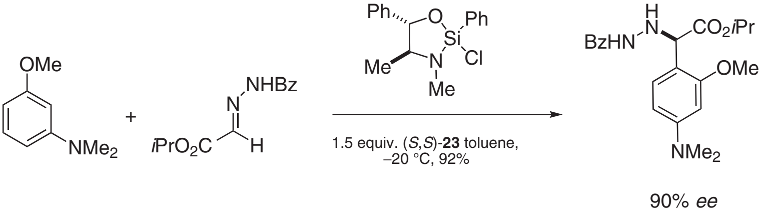
In addition, Leighton reported an allylation of benzoyl hydrazone by using the allylic silane reagent **22** giving a tertiary carbinamines with high enantioselectivity in 24 h (Scheme 16.15) [58]. This reaction is remarkable, since high enantioselectivity was achieved although a diastereomeric mixture of the allylating reagent **22** was used. Two possible explanations were given [48]. First, by using a 1.5 equiv. excess of **22**, only the major diastereomer transfers an allyl group and the minor remains unreactive. Second, the reaction proceeds through a hypervalent silicon intermediate, which is prone to a pseudorotational process. More likely, the stereogenic silicon rapidly epimerizes and only one diastereomeric intermediate transfers the allyl group.



Scheme 16.15

Imidazoles/benzimidazoles and chiral carbinamines are highly desirable compounds [59, 60]. A method for an enantioselective imidazole directed allylation of aldimines and ketimines [61] with an analog of **22** has been reported.

Extending the application of his strained silacycle reagents, Leighton *et al.* published a procedure for the enantioselective Friedel–Crafts alkylation with benzoyl hydrazones, catalyzed by a simple chiral silane Lewis acid. The enantiopure silanes were prepared in bulk in a single step from (*S,S*)- or (*R,R*)-pseudoephedrine and $PhSiCl_3$. After use in the catalytic reaction the pseudoephedrine was recovered in nearly quantitative yield during the workup. Scheme 16.16 shows the best example, in which by employing enantiopure silane **23** a 92% yield and 90% ee of the product was obtained in 48 h [62].



Scheme 16.16

Although 1.5 equiv. of the catalyst had to be used good results were obtained with heteroarenes in the alkylation reactions. A simple, plausible mode for the enantioselectivity of the Friedel–Crafts reaction has been shown (Figure 16.3). It can be seen from the proposed transition state that the arene would approach from the front (*Si*) face, as the back (*Re*) face is blocked by the phenyl group present on the silicon.

Furthermore, Leighton *et al.* reported the enantioselective [3+2] acylhydrazone-enol ether cycloaddition reaction by employing the same pseudoephedrine-based chiral silane **23.** The pyrazolidine product was isolated in 61% yield with 6 : 1 dr and 77% ee in 24 h. The application of *tert*-butyl vinyl ether led to improved diastereoselectivity and enantioselectivity (Scheme 16.17) [63].

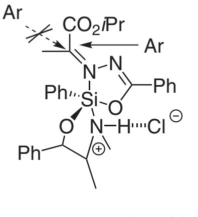
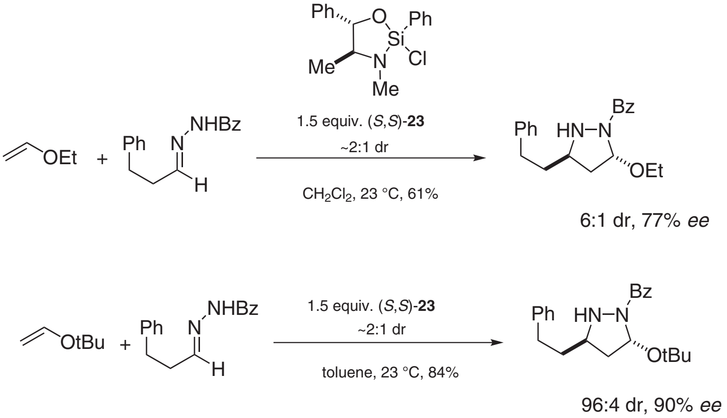
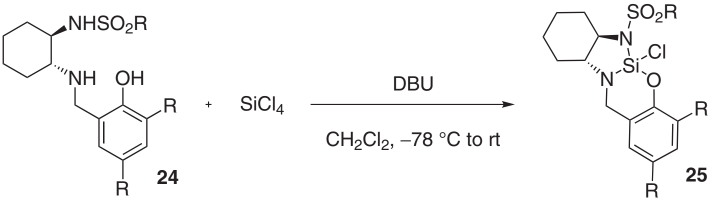


Figure 16.3 Plausible mode for the enantioselectivity of the Friedel–Crafts reaction.



Scheme 16.17

Leighton *et al.* also reported that a chiral ligand carrying three functional groups for attachment to tetrachlorosilane proved to be a good ligand for the efficient silane catalyst **25** in the cycloaddition reaction of enals with cyclopentadiene. The catalyst was generated *in situ* by treatment of **24** with $SiCl_4$ and DBU in 4h (Scheme 16.18) [64]. It was possible to assign the relative configuration of compound **25** at the silicon center by the observation of NOE interactions (Figure 16.4a).



Scheme 16.18

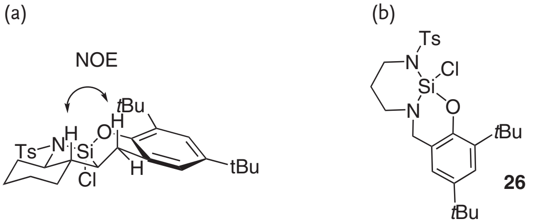
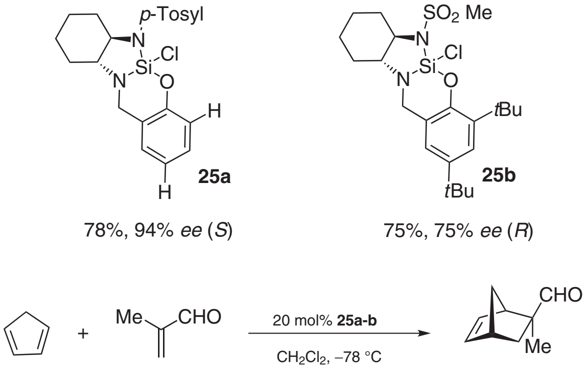


Figure 16.4 (a) Relative configuration of compound **25** at the silicon center, assigned by observation of NOE interactions; (b) strain-free six-membered silane **26**, which showed no catalytic activity.

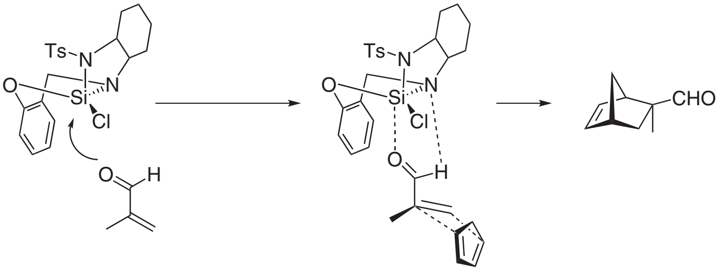
Small changes to a sulfonamide group and substituents on the phenols had a large influence on the enantioselectivity in the reaction (Scheme 16.19).



Scheme 16.19

The five-membered strained ring is very important for the Lewis acidity. The six-membered silane **26**, for example, is strain free and showed no catalytic activity under identical reaction conditions (Figure 16.4b).

Scheme 16.20 shows a possible mechanism. The aldehyde coordinates to the silicon atom and is therefore activated. The transition state is stabilized via a hydrogen bond between the aldehyde function and the benzyl substituted tertiary nitrogen atom. The benzyl group ensures that the cyclopentadiene attacks the dienophile only from one side.

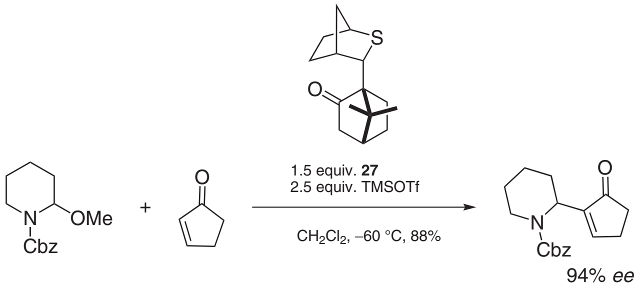


Scheme 16.20

We discuss next an example of the Morita–Baylis–Hillman reaction, where a silyl species functions as a Lewis acid co-catalyst. It would have been possible to present these examples in the previous section as silyl cation based catalysts.

However, because the enantiomeric induction is due to the enantiopure Lewis base, the examples are shown here.

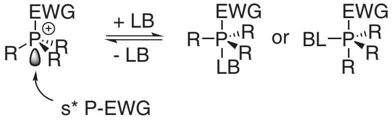
The so-called chalcogenide Morita–Baylis–Hillman reaction was first catalyzed with a sulfide and $TiCl_4$ for dual Lewis acid–base activation. Thereafter, $TiCl_4$ was replaced by TBDMSOTf [65]. An asymmetric version of the Baylis–Hillman reaction was carried out by using a chiral sulfide in place of SMe_2. Up to 94% ee and 88% yield were obtained in 5 h (Scheme 16.21) [66].



Scheme 16.21

16.4
Phosphonium Cation Based Catalysts

In 2006 Terada and Kouchi published their results on an investigation of phosphonium salts in catalysis [67]. A pentacoordinated phosphorus atom is a hypervalent [68] atom. It has a formal valence shell of more than eight electrons. As depicted in Scheme 16.22, it is possible for the lower lying σ^* orbital of a P^+–EWG (electron-withdrawing group) bond to take up a free electron pair of a Lewis base. The newly formed bond is trans to the EWG and the formed complex is more stable.



Scheme 16.22

The authors prepared a series of different phosphonium salts, a few examples of which are given below. They all incorporated electron-withdrawing groups as shown in Figure 16.5.

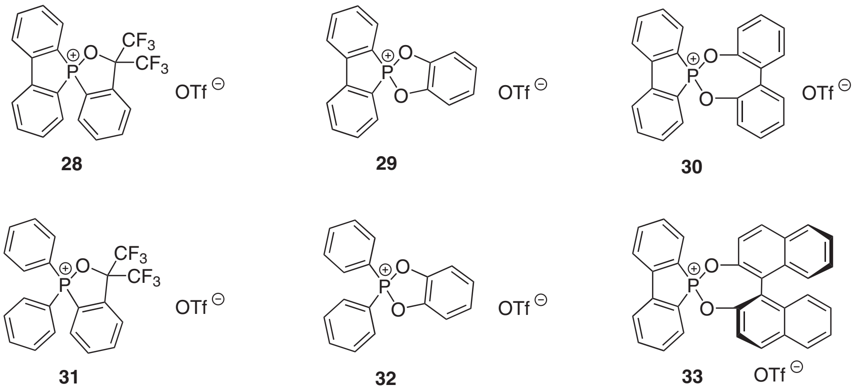
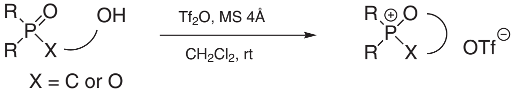


Figure 16.5 Examples of phosphonium salts used.

The salts were synthesized from hydroxy phosphine oxides or phosphinates after 1 h (Scheme 16.23). The reaction with trifluoromethanesulfonic anhydride in the presence of 4 Å molecular sieves was followed by ^{31}P NMR. The formation of the phosphonium salts was observed due to downfield shifts. It was not possible to isolate the salts; hence they were prepared *in situ* and applied in the catalytic reactions.



Scheme 16.23

In NMR investigations of the salts with DMF, it was possible to observe a shift change in the case of salts **29** and **32.** The other salts showed no change. It was found that the five-membered ring of the catechol substituent is crucial for high reactivity. That cyclic five-membered phosphorous compounds possess an enhanced reactivity is well known [69, 70]. Salt **29**, incorporated two five-membered rings and showed a stronger interaction with DMF than salt with **32.** As shown in Figure 16.6, an NOE was found between the C3 proton of the catechol moiety and the formyl proton of DMF.

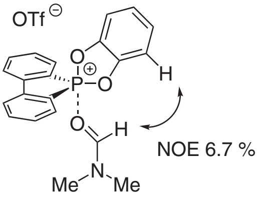
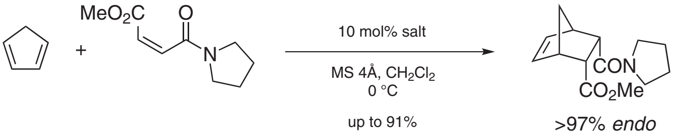


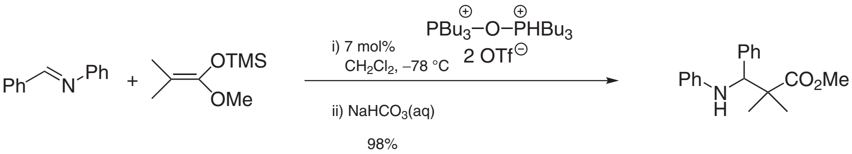
Figure 16.6 NOE found between the C3 proton of the catechol moiety in **29** and the formyl proton of DMF.

The catalytic behavior of the salts was explored in the Diels–Alder reaction. The observed catalytic activity was similar to the results of the NMR experiments. As shown in Scheme 16.24, the salts gave up to 91% yield in high *endo*-selectivity with cyclopentadiene and an unsaturated amide after 4 h. The best yield was found with salt **29**. In contrast salt **31** gave only 7% and salt **33** gave only trace amounts.



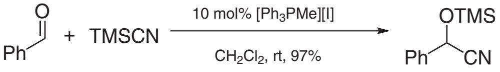
Scheme 16.24

Prior to the studies discussed above, Mukaiyama *et al.* explored in 1989 the behavior of phosphonium salts as Lewis acid catalysts. It was shown that the aldol-type reaction of aldehydes or acetals with several nucleophiles and the Michael reaction of α,β-unsaturated ketones or acetals with silyl nucleophiles gave the products in good yields with a phosphonium salt catalyst [71]. In a similar study by the same group a bisphosphonium salts (Scheme 16.25) was used as a catalyst for the synthesis of β-aminoesters [72]. High yields of up to 98% were reached in the reaction of *N*-benzylidene-aniline with the ketene silyl acetal of methyl isobutyrate. The bisphosphonium salt was found in this reaction to be a better Lewis acid catalyst than $TiCl_4$ and $SnCl_4$, which were deactivated by the resulting amines.



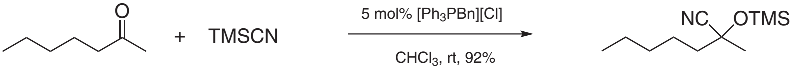
Scheme 16.25

In addition, phosphonium salts were reported by the group of Plumet to catalyze the TMSCN addition to aldehydes [73] and ketones [74]. Methyl(triphenyl)phosphonium iodide [73] was an active catalyst for the addition of TMSCN to aldehydes at room temperature. The yields after 24 h were between 70% and 97%, depending on the aldehyde applied in the reaction (Scheme 16.26). However, the salt did not catalyze the addition of TMSCN to ketones. An exception was the highly reactive cyclobutanone [75].



Scheme 16.26

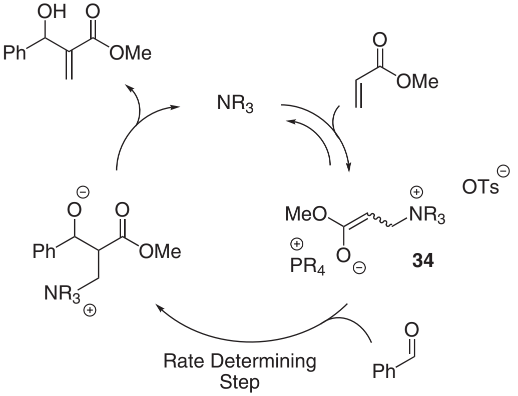
Tian *et al.* showed later that other ketones can be applied in the reaction [74] when benzyl(triphenyl)phosphonium chloride was used as the phosphonium salt based catalyst. The desired product was obtained in 92% yield in the reaction of 2-heptanone with TMSCN in 24 h (Scheme 16.27). The authors pointed out that it was essential to apply the chloride salt in the reaction. When a bromide analog was used, a very low yield of 2.6% was observed.



Scheme 16.27

Phosphonium iodide and chloride salts can be seen as bifunctional catalysts. The TMSCN addition to aldehydes and ketones can undergo a double activation. Not only the activation of the ketones or aldehydes with the phosphonium cation is necessary, but also the activation of the TMSCN by the soft Lewis base [I] or the harder Lewis base [Cl], which can form a pentavalent silicon intermediate [76].

In addition, phosphonium salts have also been reported as co-catalysts in the DABCO catalyzed Baylis–Hillman reaction of methyl acrylate with benzaldehyde [77]. Good results were found with triethyl(*n*-butyl)phosphonium tosylate, affording up to quantitative yields in some cases. The authors proposed that the phosphonium salt stabilizes the intermediate **34**, shown in Scheme 16.28, and thereby increases its concentration rather than activating the benzaldehyde.



Scheme 16.28

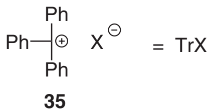
Finally, achiral phosphonium salts have been explored as Lewis acid catalysts in some other reactions. The examples are briefly listed here but are not discussed in more detail. Phosphonium salts have been used as catalysts for the *N,N*-dimethylation of primary aromatic amines with methyl alkyl carbonates, giving the products in good yields [78]. Furthermore, acetonyl(triphenyl)phosphonium bromide has been used as a catalyst for the cyclotrimerization of aldehydes [79] and for the protection/deprotection of alcohols with alkyl vinyl ethers [80, 81]. Since the pK_a of the salt is 6.6 [82–85], the authors proposed that alongside to the activation of the phosphonium center, a Brønsted acid catalyzed pathway is possible.

In summary, there are now several reported examples of phosphonium salt based Lewis acids as catalysts. Good catalytic activities have been observed. However, an asymmetric catalyzed reaction with an enantiopure phosphonium salt has not been published, yet.

16.5
Carbocation Based Catalysts

Carbocations were discovered over 100 years ago and have been investigated in diverse ways both spectroscopically and computationally [86–88]. Although as cations they can possess strong Lewis acidic character, carbocations remain seldom represented in organocatalysis, unlike the analogous of silyl salts, for example, discussed above. The first catalytic application of a carbenium salt, the trityl perchlorate **35** (Figure 16.7), was reported for Mukaiyama aldol-type reactions and Michael transformations (Scheme 16.29) [89–97].

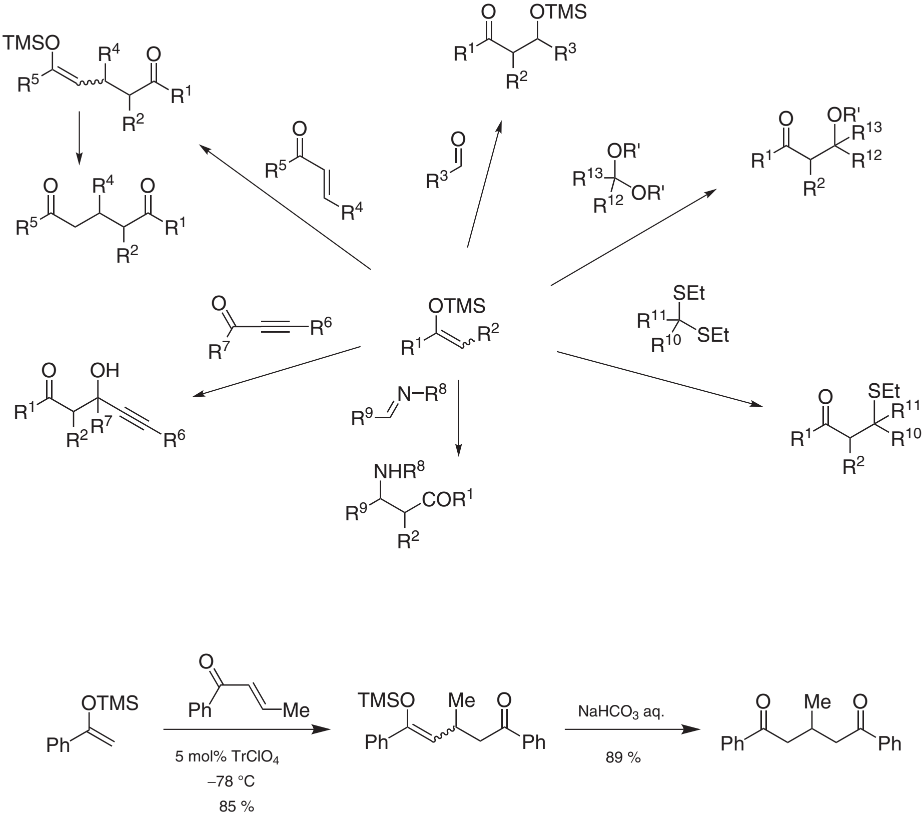
The reactions were catalyzed under mild conditions in a short time. The silyl enol ethers reacted with activated acetals or aldehydes at −78 °C to give predominantly *erythro*- or *threo*-products, respectively [91, 92]. In the same way the aldol reaction of thioacetals, catalyzed by an equimolar amount of catalyst, resulted in γ-ketosulfides [94] with high diastereoselectivity. The interaction of silyl enol ethers with α,β-unsaturated ketones, promoted by the trityl perchlorate, was shown to proceed regioselectively through 1,2- [96] or 1,4-addition [93]. Trityl salts were also


$Ph_3C^{\oplus}\ X^{\ominus} = TrX$

35

X = ClO_4,TfO, $SbCl_4$, BF_4

Figure 16.7 The first carbenium salt to find application in catalysis.

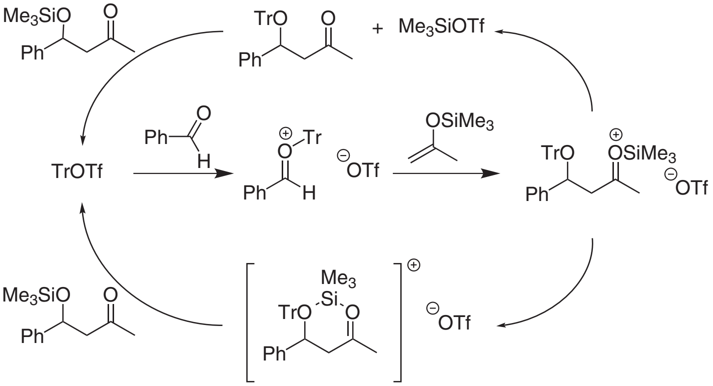


Scheme 16.29

used as Lewis acid catalyst for the synthesis of β-aminoesters [97] from the ketene silyl acetals and imines, resulting in high stereoselective product.

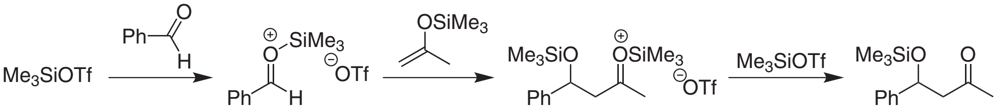
A possible mechanism of the aldol-type Mukaiyama reaction and the Sakurai allylation was investigated [98–100]. The proposed mechanism involves the catalytic activation of the aldehyde and its interaction with the silyl ketene acetal or allylsilane, resulting in an intermediate. Thereafter two possible pathways can lead either to the release of TMS triflate salt and its electrophilic attack on the trityl group in the intermediate or to the intramolecular transfer of the TMS group to the aldolate position, resulting in the evolution of the trityl catalyst and the formation of the product (Scheme 16.30). To explore both possibilities a series of experimental and spectroscopic studies were performed.

The mechanism was studied by the group of Bosnich [98]. Owing to isolated by-products in the reaction mixture a possible mechanism of the catalysis was proposed. It is possible that the aldolization and allylation reactions proceed with the evolution of TMS salt that is itself a strong Lewis acid and can catalyze the



Scheme 16.30

reaction at a high rate, after the initial activation of the carbocation (Scheme 16.31). The possible sources of TMS salt production in the reaction were investigated. The utilization of a hindered base suppressed the influence of the silyl salt, and the rate of the reaction was dramatically diminished. This consequence was considered to confirm that the TMS salt can catalyze the reaction even in the undetectable quantities of 10^{-7} mol.



Scheme 16.31

Chen *et al.* investigated functionalized trityl cations with different counter anions and TMS or TBS enolates [100] and introduced the dibenzosuberone-derived salt **36 [101]** as a catalyst (Figure 16.8).

The TBS ketene acetal is a better silyl component, because the rate of the TBS transfer to the aldolate group of the product decreased and did not overtake the slow-acting carbenium catalysis (Scheme 16.32).

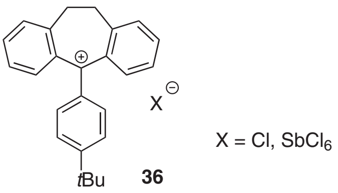


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Figure 16.8 A dibenzosuberone-derived salt employed as a catalyst.

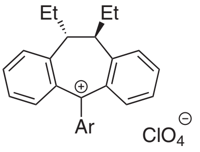

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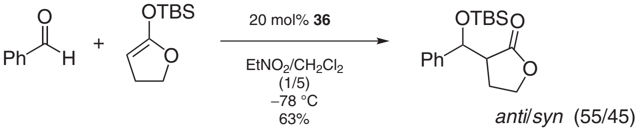
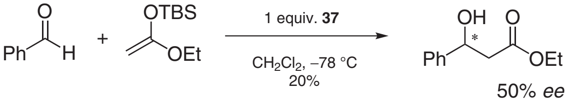
Figure 16.9 An enantiopure trityl salt prepared as a catalyst.



Scheme 16.32

Thereafter, the group of Chen [102] prepared the enantiopure trityl salt **37** and thus could support their proposed mechanism of catalysis (Figure 16.9). Since an enantiomeric excess was found, carbenium-mediated catalysis had to occur.

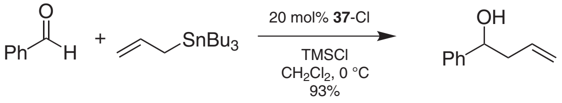
When the reaction time was increased from 3 to 6 h the enantioselectivity of the aldolization with catalyst **37** decreased from 24% to 11% along with an increase of yield from 52% to 99%. The decrease in enantioselectivity with longer reaction time indicates an increasing silyl-mediated catalysis, due to the slow metathesis between tritylated aldolate and silyl salt. The best enantioselectivity of 50% together with a low yield of 22% was obtained when 1 equiv. of catalyst **37** was used (Scheme 16.33).



Scheme 16.33

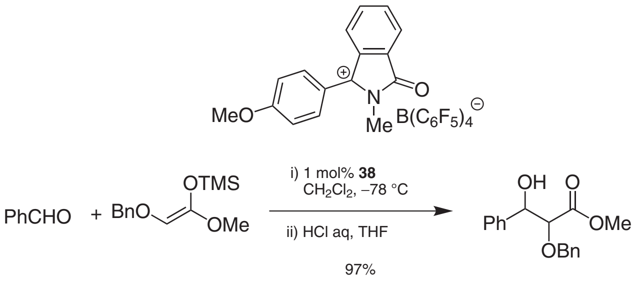
The conditions used to suppress silyl-mediated catalysis and to increase the carbenium catalysis is important in introducing the asymmetric information into the product. The rigid conformation and the enhanced reactivity of the carbocation was an important requirement for the asymmetric carbenium catalyzed aldol-type addition.

In addition, catalyst **37** was explored in the allylstannane addition to aldehydes [103]. In this allylation process the trityl chloride **37**, due to its disposition to partially ionic character of the halogen bonding, was employed as a catalyst in a complementary tandem with the weak Lewis acid TMSCl (Scheme 16.34). The excess of the silyl component was necessary, to release the trityl catalyst from the intermediate to complete the catalytic cycle. The achieved yield was 93%, when trityl chloride **37** was applied.



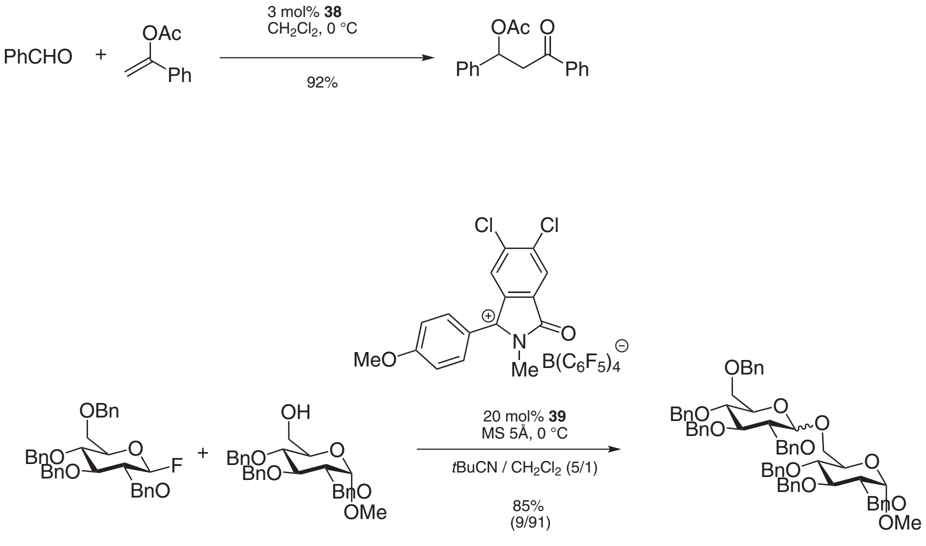
Scheme 16.34

To enhance the catalytic activity of a carbocationic center, the Lewis acid **38** was prepared by Mukaiyama [104, 105]. The 1-oxoisoindolium-based carbenium salt **38** [106] has a weakly coordinating borate counter anion in order to increase the catalytic activity of the cation in an aldolization (Scheme 16.35) [104]. The Mukaiyama aldol reaction was catalyzed by 1 mol% of salt **38** with a yield of 97% in 30 min.



Scheme 16.35

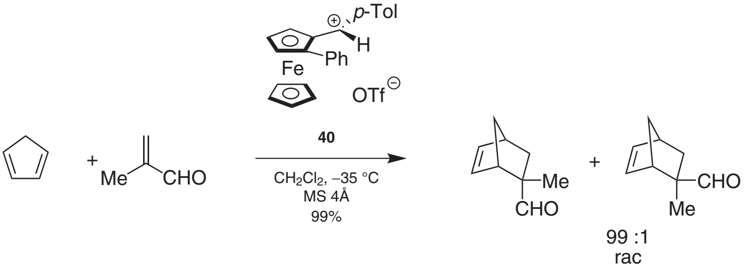
The catalytic activity of the oxoisoindolium salts **38** and **39** were also compared to that of trityl tetrakis[pentafluorophenyl]borate in the addition reaction of enol acetate to benzaldehyde and a glycosylation reaction (Scheme 16.36) [105, 107].



Scheme 16.36

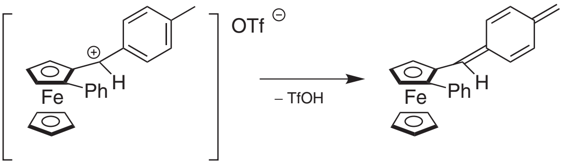
Compound **38** gave in the aldolization the product in higher yield of 92% after 30 min, compared to the trityl catalyzed reaction, which resulted in a yield of 73%. Similar results were observed in the glycosylation reaction: 85% (α : β ratio 9 : 91) and 72% (α : β ratio 10 : 90) respectively. The application of the highly hindered tetrakis[pentafluorophenyl]borate anion is advantageous for the stabilization of the positive charge in carbocation **38** and at the same time promotes its accessibility to the interaction with a carbonyl species.

The synthesis of the stable α-ferrocenyl carbocations **40** led to further investigation of carbenium salts catalyzed reactions (Scheme 16.37). Kagan *et al.* [108–110] designed the *o*-substituted ferrocenyl scaffold that allowed them to avoid the placement of two aryl groups on the carbocation and provided the stabilization and asymmetry, preventing isomerization by facile rotation about the carbenium center. Catalyst **40** was applied in the Diels–Alder reaction of cyclopentadiene with methacrolein and resulted an excellent *exo/endo* diastereoselectivity of up to 99 : 1 in the presence of 4 Å MS in nearly quantitative yield (Scheme 16.37).



Scheme 16.37

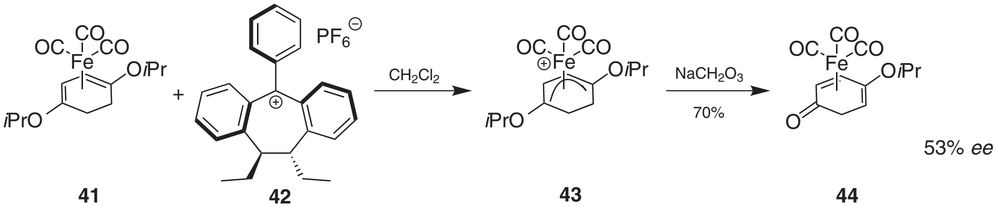
However, Sammakia and Latham [111] reported that the reaction can actually be catalyzed by the protic acid TfOH, released either by decomposition of the carbenium salt or by nucleophilic attack of the diene on the cation center with evolution of the proton (Scheme 16.38).



Scheme 16.38

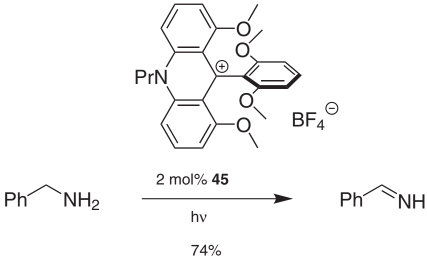
Additional studies of the mechanism were carried out. The influence of the reaction rate on the nature of the environment at the cationic carbon showed that concurrent formation of the protic acid proceeds, if the substituents can undergo isomerization (Scheme 16.38). Therefore, carbenium catalysis with salt **40** is negligible. It was shown that the reaction was still catalyzed even when a base was added, to rule out a TfOH-catalyzed reaction. In that case the protonated base was the catalyst.

Scheme 16.39 shows another application of a carbocation. Owing to the extensively represented oxidative behavior of the carbenium ions as hydride abstractor or one-electron oxidant [112], the carbocation **42** was used as a reagents in this reaction. More recently, the enantioselective outcome in a hydride transfer reaction was reported [113, 114]. Abstraction of the *exo* hydrogen atoms from the tricarbonyliron complex **41** resulted in a yield of up to 70% and enantioselectivity of 53% (Scheme 16.39) [113].



Scheme 16.39

In addition, the oxidative behavior of the acridinium carbocations **45** was investigated by the group of Lacour in a photoinduced electron transfer reaction [115]. The use of 2 mol% of the achiral hindered acridinium salt **45** catalyzed the aerobic photooxidation of the primary benzylic amine to benzylimine in 74% yield (Scheme 16.40).



Scheme 16.40

At present, only one example of an asymmetric catalyzed reaction with an enantiopure carbocation based salt is known. In this section it has been shown that a good knowledge of a catalyzed reaction is necessary. Achiral side reactions can have a critical negative influence. Nevertheless, carbocations can be highly active catalysts. However, this sometimes makes their application difficult.

In the next section ionic liquids will be discussed briefly, some of which can also be considered as carbocation-based salts. They are far more stable but, on the other hand, have a lower catalytic activity.

16.6
Ionic Liquids

Ionic liquids are salts that have, per definition, a melting point below 100 °C. If their melting point is below room temperature they are called room temperature ionic liquids (RTIL). The latter have attracted much interest in recent years as novel solvents for reactions and electrochemical processes [116]. Some of these liquids are considered to be "green solvents" [117]. The most commonly used liquids are based on imidazolium cations like 1-butyl-3-methylimidazolium [bmim] with an appropriate counter anion like hexafluorophosphate [PF_6]. Many ionic liquids are known to accelerate reactions. In most cases, achiral ionic liquids are applied and have been reviewed [116]. Here, the few examples of chiral ionic liquids (CILs) as catalysts are discussed.

There have been several quite recent reviews on the preparation and application of chiral enantiopure ionic liquids [118–121]. However, evaluation of the growing number of enantiopure ionic liquids was often focused more on their behavior as chiral discrimination agents. Hence, the number of examples of reactions catalyzed by enantiopure ionic liquids is rather limited. Therefore, this section gives only a brief overview of chiral ionic liquids. Importantly, chiral ionic liquids are different to task-specific ionic liquids (also called functionalized ionic liquids). Figure 16.10 presents a very successful example of a task-specific ionic liquid (**46**). This catalyst with a loading of 15 mol% under neat conditions gave up to 100% yield and 99% ee in the Michael addition of cyclohexanones to nitroolefins [122]. This catalyst belongs to the field of the proline-catalyzed reactions.

Howarth *et al.* [123] published in 1997 a report on the preparation of ionic liquids **48** and **49.** They showed that imidazolium cations can be used as Lewis acid centers in catalytic amount rather than as solvent (Scheme 16.41). The bromide salts **48a** and **49** were prepared by a literature procedure [124] from TMS protected imidazole **47** and ethyl bromide or (*S*)-1-bromo-2-methylbutane in refluxing toluene in 46% and 21% yield, respectively. Salt **48a** was converted into salt **48b** with $AgCF_3COO$ in 89% yield.

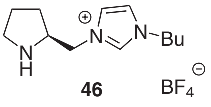


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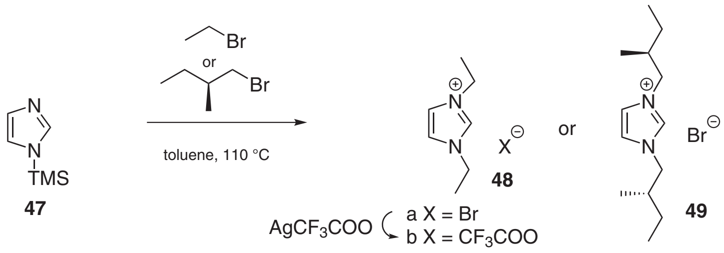
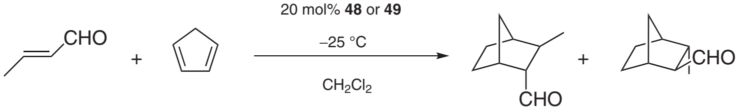
Figure 16.10 Example of a task specific ionic liquid.



Scheme 16.41

The salts catalyzed the Diels–Alder reaction of crotonaldehyde with cyclopentadiene (Scheme 16.42). The obtained yields were 35–40% with an *endo* : *exo* ratio of 90 : 10. The control reaction without the salt at −25 °C gave no product. The observed ee with the enantiopure salt **49** was less than 5%. However, this was the first example to show that imidazolium-based ionic liquids can be used in substoichiometric amounts as Lewis acid catalysts.



Scheme 16.42

Welton *et al.* explored first the origin of the catalytic activity of imidazolium-based ionic liquids [125], and performed studies in which they proposed that hydrogen bond activation plays an important part in the activation of a dienophile in the Diels–Alder reaction. This was proposed to be due to observed hydrogen bonds between the imidazolium cation and the corresponding counter anion in the salt. The reaction of methyl acrylate in the ionic liquid [bmim][BF_4] with cyclopentadiene gave the product in 72 h at 25 °C (85% yield). When the C2-methylated salt [bm_2im][BF_4] was used as solvent, a similar yield of 84% was obtained; however, the *endo* : *exo* ratio changed from 4.6 to 3.3. This was attributed to weaker hydrogen bond formation with the C4 and C5 protons compared to the C2 proton in the first salt (Figure 16.11).

Hence, it would be possible to consider imidazolium-based ionic liquids as hydrogen bond activator organocatalysts, which will be discussed in another chapter.

The ionic liquid [bmim][BF_4] can catalyze the aza-Diels–Alder reaction in the synthesis of pyrano- and furanoquinolines [126]. This reaction was also catalyzed by the enantiopure bis-imidazolinium salt **50** in 67% yield with an *endo* : *exo* ratio of 60 : 40 (Scheme 16.43) [127]. The product was isolated as a racemate. In addition, the aza-Diels–Alder reaction with imines and Danishefsky's diene catalyzed by the salt **50** gave racemic product. The salt and its analogues could be easily prepared

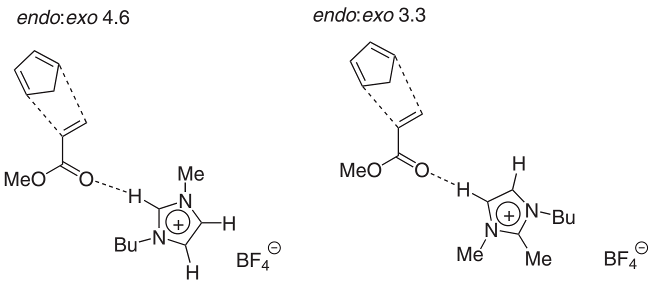
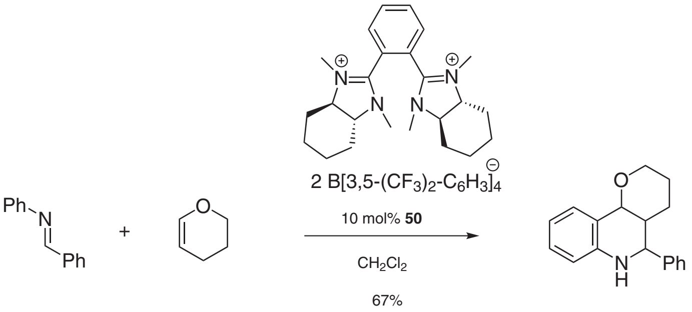


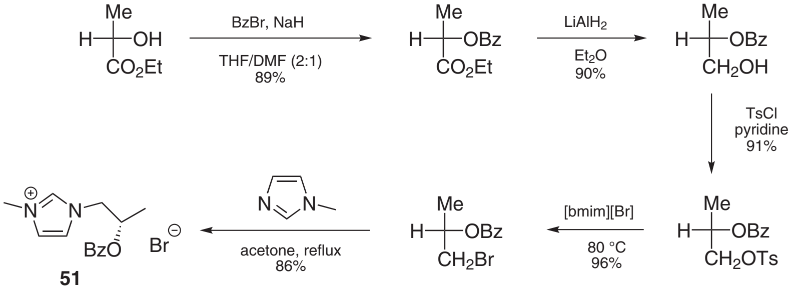
Figure 16.11 Proposed hydrogen bond activation of a dienophile in the Diels–Alder reaction.



Scheme 16.43

via oxidation of the corresponding aminals [128]. The influence of the counter anion in achiral C2-substituted imidazolinium salts, which can be also described as 4,5-dihydroimidazolium or saturated imidazolium salts, was explored in the aza-Diels–Alder reaction. It was shown that the catalytic activity increased with the more lipophilic counter anion, and therefore the more hydrophobic the salt became [129].

The enantiopure ionic liquids **51** and **52** were prepared quite recently and explored in the Michael addition [130]. Scheme 16.44 shows the synthetic route to salt **51**. The salt was obtained in an overall yield of 60%.



Scheme 16.44

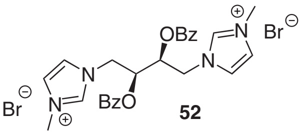


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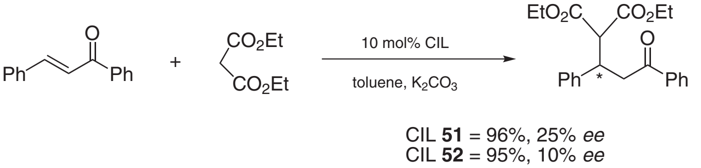
Figure 16.12 An enantiopure ionic liquid recently prepared and then used in the Michael addition reaction.

Salt **52** was prepared in a similar way from L-(+)-diethyl tartrate in an overall yield of 44% (Figure 16.12).

Salt **51** gave a yield of 96% and 25% ee at room temperature (Scheme 16.45). Because the melting point of the salt is 40 °C, toluene was used as a solvent. The incorporation of different anions in the salt had only a small influence on the result. Compared to the [Br] counter anion, $[PF_6]$ resulted in 23% ee and $[BF_4]$ gave an ee of 24%. The polar solvents DMSO and DMF gave lower ee's of 17% and 16%, respectively. Salt **52** with toluene gave a lower ee of 10%.



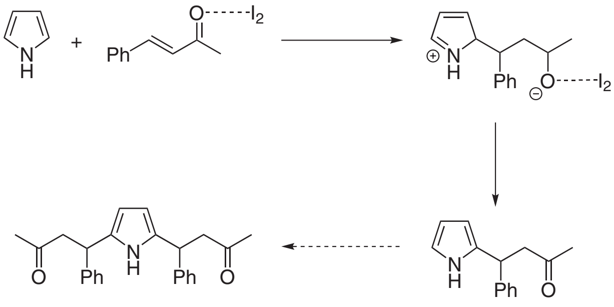
Scheme 16.45

Chiral ionic liquids have also been applied in the Baylis–Hillman reaction [131, 132]. Since they were used as co-catalyst and the asymmetric induction is considered to be achieved by the formation of ion pairs, they will not be discussed in detail here.

Examples of enantiopure ionic liquids applied successfully as asymmetric catalytic reaction media are still very limited. However, considering the large number of possible applications in combination with the advantages of easy recoverability, it is an important task to develop this research further.

16.7
Miscellaneous Catalysts

Iodine can be used as a mild Lewis acid catalyst. Owing to its achiral nature only one example shall be shown here. Notably, though, several other examples have been reported in the literature. Iodine can, for example, catalyze the addition of pyrroles to α,β-unsaturated ketones (Scheme 16.46) [133]. Pyrrole and 3 equiv. of ketone resulted in disubstituted products in up to 92% yield in 10 min with



Scheme 16.46

10 mol% of iodine. When only 1.1 equiv. of ketone was applied in the reaction, mono- and disubstituted products were formed in a few minutes in up to 95% yield with a ratio between 1 : 1 and 1 : 5.

In 2007 Ishihara *et al*. [134] published the application of a "chiral iodine atom" through the reaction of NSI and an enantiopure nucleophilic phosphoramidite for the halocyclization of homo(polyprenyl))arenes.

Tetracyanoethylene and dicyanoketene acetals and derivatives are another class of neutral Lewis acids. They can catalyze a reaction due to their π-Lewis acidity. They promoted, for example, the alcoholysis of epoxides [135] and the carbon–carbon bond formation of acetals [136, 137].

16.8
Conclusion

This chapter has presented Lewis acid organocatalysts. They can catalyze, as do their metal counterparts, a broad range of reactions. However, in most cases the asymmetric induction is low or only racemic product can be obtained so far. Organic Lewis acids are either very active or in case of the stable ionic liquids less active. The more active they are, the more moisture sensitive they are. This research is still at the beginning in terms of asymmetric induction and much room for improvement is left compared to the other well-established types of organocatalysts.

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Part II
Asymmetric Catalysis with Covalent Interactions

17
Rationalizing Reactivity and Selectivity in Aminocatalytic Reactions

Raghavan B. Sunoj

17.1
Introduction

Over the years, the growth of various forms of chemical catalysis has been driven by the increasing demand for efficient processes. In the last few decades, the quest for environmentally benign protocols have received more attention. While most catalysts that are in use today belong to the transition metal family, the last decade has witnessed an unprecedented development in the area of organocatalysis [1]. The use of small molecules as promising candidates toward catalyzing organic reactions came into reckoning not too long ago, though the origin of the basic ideas was arguably submerged for some decades. The probable reason for the lack of early popularity could be attributed to poor stereoselection in the formative years. The real impetus for modern organocatalysis originated from the works of several groups in the early part of the last decade. The vital conceptual developments as well as diverse applications of organocatalysis were due to List, Barbas, Denmark, Jacobsen, Jorgensen, MacMillan, Hayashi, and others [2]. The basic reason behind the contemporary popularity of modern organocatalysis derives from it being catalytic and stereoselective. This implies that in addition to making use of the catalytic abilities of small molecules the reaction can also be made to yield good stereoselectivity.

An understanding of enzymatic catalysis has served as a source of inspiration to chemists that led to the invention of several enzyme mimetics. The field of organocatalysis has received its share of motivation by closely examining the aldolases family of enzymes [3]. It has been widely believed that intermediates such as carbinolamine and enamines (popularly known as Schiff's bases) are formed in the enzymatic steps. While the involvement of these intermediates has been confirmed through high-resolution crystallographic methods in biological systems (see below), their counterparts in organic chemistry remained elusive until recently.

The underlying theme encompassing all these catalytic reactions is the initial activation of a substrate to a better nucleophile or electrophile. Such activated substrates exhibit an increased propensity to form new chemical bonds. It is,

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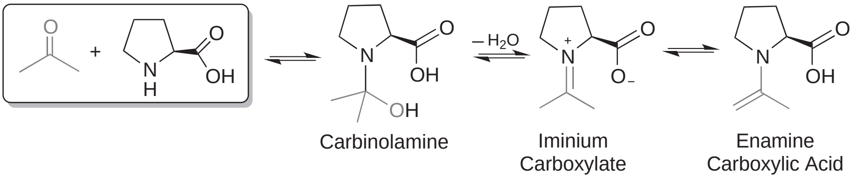
therefore, fundamental to establish the molecular origins of such substrate activations to gain an improved understanding of organocatalysis. This chapter aims to bring out molecular-level details of the formation of key intermediates as well as establishing how these influence the mechanism and stereochemical course of the reaction. The intention has been to avoid an exhaustive literature review and remain focused on conveying the vital messages with the help of selected examples, as summarized in the following sections.

17.2
Secondary Amine Catalysis

Covalent activations of substrates can be achieved through different methods. One such method includes the formation of intermediates between an otherwise relatively inert substrate and the catalyst. This is comparable with the formation of an "enzyme–substrate" complex in an enzymatic reaction. In organocatalytic reactions, the substrates can be classified as nucleophilic and electrophilic partners. Each of these substrates can be activated by interactions with the catalyst. The catalyst–substrate interaction can either be covalent or non-covalent. While the non-covalent activations are described elsewhere in other chapters of these volumes, the focus herein is on covalent activations. In covalent activation, the substrate forms a bond with the catalyst and thereby becomes activated. For instance, in the following example of the formation of the proline enamine of acetone the substrate (acetone) reacts with proline to generate the activated nucleophile (enamine) (Scheme 17.1).



Scheme 17.1 Formation of (a) proline-enamine (b) dimethylamine-enamine.

17.2.1
Mechanism of Secondary Amine Catalysis

The following section presents the energetic details of the formation of such activated substrates as well as how the stereoselectivity is imparted in the subsequent step of the reaction. The illustrations generally revolve around simple amines, pyrrolidines, and proline. Though a broad range of substrates has been considered, to maintain some degree of uniformity the substrates described here are generally simple aldehydes, ketones, nitroolefins, and other activated olefins.

17.2.1.1 Important Intermediates in Amino Catalysis

The generally accepted mechanism of secondary amine catalysis involves the activation of reactants in the form of enamine or iminium intermediate. For instance, when a reaction such the one in Scheme 17.1 is considered, the nucleophilic partner first forms an enamine with proline (or other secondary amines). The energetics of formation of enamine/iminium intermediates has been studied by using computational methods. In one of the very first reports, Boyd and coworkers employed DFT(B3LYP) method to examine the elementary steps for the formation of enamine between proline and acetone [4]. Though the net reaction appears like a direct formation of enamine, there are several likely scenarios that have been considered. The initial addition of proline to acetone is suggested to give rise to a putative carbinolamine intermediate. Computed barrier for carbinolamine formation indicated that the transfer of amino proton is more preferred over the carboxylic acid proton. The dehydration of carbinolamine subsequently furnishes an iminium carboxylate intermediate, which upon intramolecular proton transfer gives the desired enamine intermediate.

In this mechanistic proposal, the role of carboxylic acid proton in facilitating the dehydration of carbinolamine is important. For systems that lack carboxylic acid group, such as a simple dimethylamine, unsubstituted pyrrolidine and diarylprolinols, the barrier to dehydration was reported to be much higher [5]. A comparison between the dehydration steps across different available reports brings out certain interesting general trends in the barrier to dehydration. The fact that a hydroxyl group requires to be expelled from the carbinolamine intermediate, an assisted process appears desirable. In the case of proline, the dehydration is proposed to involve protonation of the hydroxyl group, rendering higher leaving ability.

Patil and Sunoj have shown that for other mono functional secondary amines that lack ability for intramolecular protonation, an external ancillary species is likely to be involved in the dehydration step [5a,b]. In the following example for the formation of enamine between dimethylamine and propanal, the addition (a) as well as the dehydration (b) transition states, as shown in Figure 17.1, were respectively found to be 24 and 47 kcal mol^{-1} at the PCM$_{(THF)}$/mPW1PW91/6-31G* level of theory in the unassisted mode. Interestingly, explicit inclusion of two molecules of polar protic solvents or additives (e.g., methanol) in the transition states, as shown in **3** and **4**, led to significant stabilization of both addition and dehydration transition states. In the methanol-assisted pathway, the addition step was found to proceed in a barrierless fashion while dehydration exhibits a barrier as low as 6 kcal mol^{-1}. The barriers computed using these refined transition state models are intuitively more appealing. In the absence of such protic additives/solvents, one of the reactants, such as the amine itself, could help stabilize the transition state for dehydration.

In another example, the formation of enamine between pyrrolidine and propanal has been examined using DFT and *ab initio* MP2 methods [5b]. Again, the computed barriers for the addition and dehydration steps were found to be lowered by considering transition states with explicit phenol/methanol (Figure 17.2). Stabilization of the initial addition transition state through a cyclic hydrogen bonded

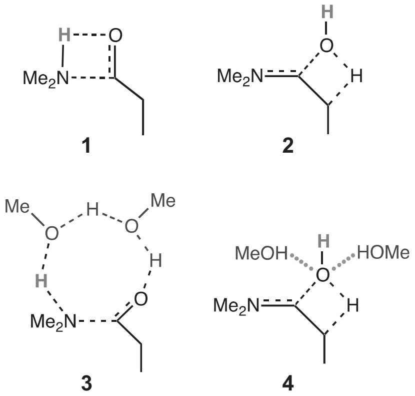


Figure 17.1 Key transition states involved in the formation of enamine intermediate between dimethylamine and propanal.

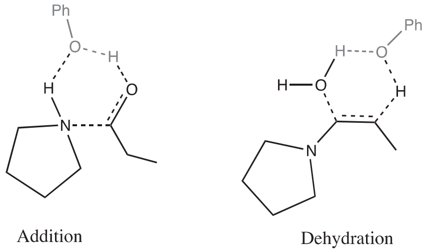


Figure 17.2 Phenol-assisted addition and dehydration transition states in the enamine formation between pyrrolidine and propanal.

network lowered the barrier to addition by 34 and 40 kcal mol^{-1} respectively for phenol-assisted and methanol-assisted models as compared to the corresponding unassisted pathway at the PCM$_{(THF)}$/mPW1PW91/6-311G**//6-31G* level of theory. Similarly, the activation barrier for the dehydration step in the unassisted pathway was estimated to be as high as 39 kcal mol^{-1}. However, a two-step phenol- or methanol-assisted dehydration could lead to a nearly barrierless process. These predictions are in agreement with an earlier report by Gellman and coworkers wherein the introduction of additives such as catechol or phenol resulted in rate enhancements in the Michael reaction between propanal and methyl vinyl ketone (MVK) with diarylprolinol ether as the catalyst [6].

Similar to the participation of enamine intermediates in several secondary amine catalyzed organocatalytic reactions, certain other types of activation through iminium ions are also suggested. The electrophilic activation of a Michael acceptor like methyl vinyl ketone (MVK) can be regarded as an example for iminium ion activation. The reaction between pyrrolidine and MVK can give rise to an activated double bond capable of functioning as an improved acceptor. Again, the generation of iminium ion requires removal of a hydroxide group from a carbon center.

Computations have revealed that direct formation of iminium could involve a high barrier whereas a protic solvent assisted pathway offers lower barriers. However, in a related series, such as, say the formation of enamine from an aldehyde and iminium from MVK, the latter is reported to be energetically more costly [5b].

For several years of developments in organocatalysis, the involvement of enamine intermediates in secondary amine catalysis has been intuitively regarded as correct while the experimental verification of its presence under the reaction conditions long continued to remain elusive. Stork enamine reactions have enjoyed widespread acceptance over the years wherein a secondary amine is employed to activate the nucleophilic partner in the form of an enamine. The enamines are then made to react with various electrophilic acceptors, leading to different manifestations such as alkylation, acylations, and so on [7]. The availability of reservoir of lone pair electrons on the nitrogen atom renders highly nucleophilic character to the β-carbon and would readily be available for bond formation with electrophiles. It has been suggested that the extent of p-orbital characteristics would help improve the ability of the lone pair to delocalize with the double bond and, thereby, increase the nucleophilic attributes to pyrrolidine enamines, as compared to the piperidine analogues. When the degree of pyramidalization at the nitrogen is lowered, the p-orbital characteristic will increase. This observation has been supported by both photoelectron spectroscopic as well as X-ray crystallographic studies [8]. All these attributes of enamines offer a somewhat perceptive feel about its participation in various reactions. It is therefore timely to examine what is the latest understanding in this domain, as summarized below.

17.2.1.2 Experimental Identification of Enamines in Organocatalysis

In what can be regarded as the earliest evidence for the participation of enamines in a proline-catalyzed aldol reaction and its *in situ* detection was provided by Metzeger and coworker. A combination of high-resolution MS/MS and ESI-MS methods could detect the condensation product between proline and acetone [9]. Furthermore, the evidence was strongly in favor of enamine as compared to the isomeric oxazolidinone. In a subsequent study, Seebach and coworkers using NMR and IR studies proposed that an oxazolidinone intermediate plays a vital role in asymmetric organocatalytic Michael reactions. Evidence for participation of bicyclic as well as spirocyclic oxazolidinones in proline-catalyzed reactions was presented [10].

The participation of enamine and iminium intermediates is also suggested to play important roles in the action of aldolase antibodies. In an important study, Heine, De Santis, and coworkers obtained ultrahigh resolution structures of carbinolamine and enamine intermediates involved in an aldolase mechanism [11]. Later, Zhu and coworkers reported the direct observation of enamine by crystallographic analysis of the adduct between an aldolase antibody (33F12) and a 1,3-diketone [12]. Gschwind, Zeitler, and coworkers have employed *in situ* NMR studies on nascent enamines derived from prolinol and prolinol ethers and aldehydes (**5**, Figure 17.3). A general preference for the (*E*)-configuration across the enamine double bond was noticed while the position of the double bond was found

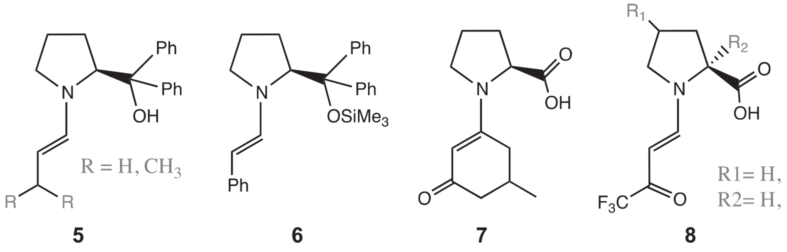
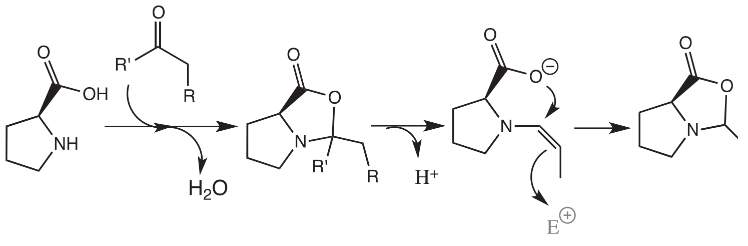


Figure 17.3 Selected examples of structurally characterized enamines.

to be *anti* with respect to the carboxylic acid group [13]. Structural determination of enamine in the solid state was reported by Seebach and coworkers [14]. Enamine **5**, formed between diaryl prolinol silyl ether and 2-phenylacetaldehyde, exhibited an (*E*) configuration of the double bond and maintained an *anti* conformation with respect to the bulky α-substituent on the pyrrolidine ring. Larger family of iminium salts with BF_4^-, PF_6^-, and other counter anions have also been prepared and characterized using standard analytical techniques, including X-ray crystallography. A general preference towards the (*E*)-configuration was noticed in the solid state while NMR studies in solutions additionally suggest that a small fraction could exist in the (*Z*)-configuration as well.

The most convincing evidence on the existence of a proline enamine came in late 2010 from List's group, who elucidated the structure of both aldehyde and ketone-derived proline enaminones (**7** and **8** in Figure 17.3) using X-ray crystallography. The enamines were found to remain in an (*E*)-configuration around the double bond, which maintains an exclusive *anti*-conformation with respect to the carboxylic acid group [15].

Equally interesting are a few reports questioning the existence of enamine as compared to an oxazolidinone intermediate. Different views prevail on the role of oxazolidinone in proline catalysis. Oxazolidinone is suggested to be an unproductive intermediate, or could be regarded as promoting a "parasitic equilibrium" under the reaction conditions [16]. In fact, List and coworkers have employed ^{1}H NMR techniques to detect oxazolidinones formed between proline and different ketones, in the absence of aldehydes [17]. Kinetic studies by Mayr and coworkers have provided additional insights into the involvement of oxazolidinones, particularly in the stereocontrolling bond formation step (Scheme 17.2) [18]. It was further

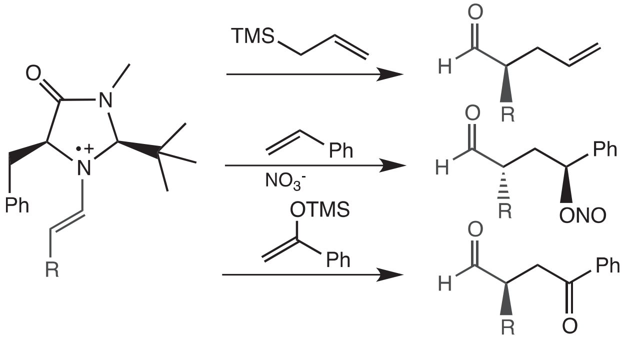


Scheme 17.2 Generation of oxazolidinone intermediate.

suggested that the carboxylate group of enamine offers anchimeric assistance in the C–C bond formation step.

17.2.1.3 **Enamine Radical Cation: The Concept of SOMO Activation**

The scope of enamine participation in organocatalytic reactions has been further extended by making use of SOMO-activation principles by the MacMillan and Nicholau groups [19]. In this approach, the enamines formed between chiral imidazolidinones and aldehydes are subjected to single-electron oxidation to generate a transient radical species, which is then made to react with various different SOMOphiles depending on the desired target (Scheme 17.3).



Scheme 17.3 Selected examples of asymmetric reactions achieved using the SOMO activation protocol.

In general, a steric control based working hypothesis, as shown in Figure 17.4, is employed towards rationalizing the stereochemical outcome of the reaction. The approach of the electrophile to the enamine is suggested to occur from the face opposite to that where bulkier groups are present. To the best of our knowledge, transition states for stereocontrolling the bond formation step with chiral imidazolidinones have not been reported to date.

Houk, MacMillan, and coworkers have employed DFT (UB3LYP and UM06-2X) methods to establish the mechanism and selectivity in intramolecular α-arylation of aldehydes that make use of SOMO activation protocol (Scheme 17.4) [20]. The

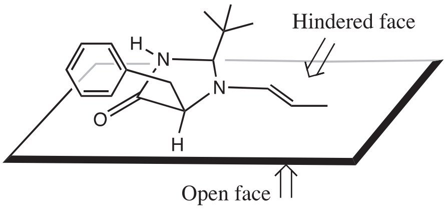
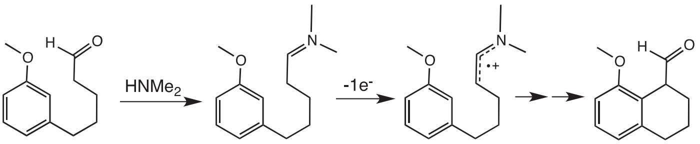


Figure 17.4 Illustration for the preferred direction of approach of the SOMOphile.



Scheme 17.4 Example of an α-arylation of aldehydes using SOMO catalysis.

cyclization of a series of aldehydes using a model system, consisting of dimethylenamine radical cation, was examined. The computations revealed that the *para* and *meta* cyclizations were more favored than *ortho* and *meta* by about 2.4–3.4 kcal mol^{-1}, which is in concordance with experimental observations.

Discussions hitherto have been on the energetic details of various modes of substrate activation leading to vital intermediates such as enamines and iminium ions. Once such reactive species are generated, the next important event in the reaction sequence is the new bond formation. The following section provides highlights of the bond-forming process, with particular emphasis on stereoselectivity issues.

17.3
Stereoselectivity in Proline-Catalyzed Reactions

A domain where successful applications of qualitative concepts derived from molecular orbital theory can be found is in the rationalization of pericyclic reactions [21]. Since the days of Woodward–Hoffman rules, MO theory remained a practical tool for organic chemists that provided the rational foundations for designing new reactions [22]. In the early days, one would resort to a range of methods such as the Hückel to semi-empirical MO theories to explain observations such as the *endo/exo* selectivity in Diels–Alder cycloadditions. With the advent of modern quantum chemical methods, as well as the unprecedented developments in hardware technology, computational quantum chemical methods have now become powerful tools to address various different chemical problems [23]. Examination of the literature over the last decade readily reveals that there has been an interesting synergism between experimental developments and accompanying computational rationalizations in the area of organocatalysis [24].

The key to the successful applications of density functional or *ab initio* computations to real-life organocatalytic reactions lies on our ability to identify the transition states for the stereocontrolling step in the reaction. Computational methods offer direct access to the structure and energetics of the vital transition states involved in competing diastereomeric pathways. The energy difference between such diastereomeric transition states, as shown in Figure 17.5, can be computed and has been found to be effective in rationalizing the stereochemical outcome of the reaction. In an asymmetric reaction capable for yielding one enantiomer in excess of the other, the enantiomeric excess can be computed by assuming a

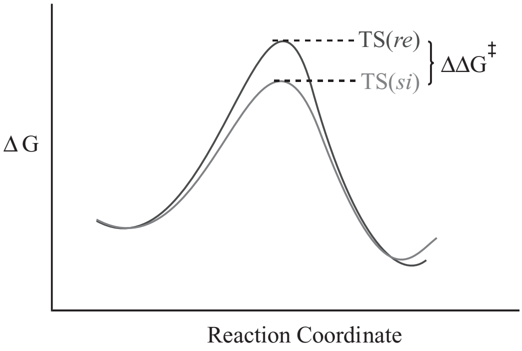


Figure 17.5 Differential stabilization of diastereomeric transition states responsible for stereoselectivity.

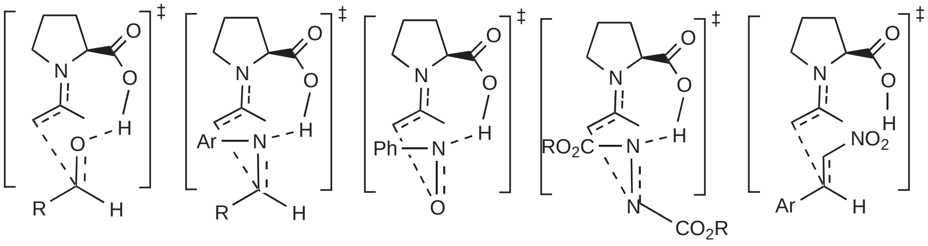
Boltzmann distribution of the competing transition states that are responsible for the final ratio between the enantiomers. If the free energy difference between pro-(*R*) and pro-(*S*) transition states are estimated at a given temperature, the %ee can be computed using the following equation:

$$\%\mathrm{ee} = \frac{1-\mathrm{e}^{\frac{-\Delta G^{\ddagger}_{R/S}}{RT}}}{1+\mathrm{e}^{\frac{-\Delta G^{\ddagger}_{R/S}}{RT}}} \times 100 \tag{17.1}$$

A more comprehensive compilation of organocatalytic reactions and its plethora of applications can be found in other chapters. While these reactions have been quite successful, one of the fundamental questions that should be addressed is on how proline acts as a successful catalyst across different types of reactions. Computational investigations using the density functional theory have been impressively useful in offering invaluable insights since the early days of developments in proline catalysis [25]. A more exhaustive treatment of how quantum mechanical studies toward understanding the mechanism and stereoselectivities flourished in the last decade was recently compiled by Houk and coworkers [26]. The following sections present a descriptive account of transition states involved in organocatalytic reactions.

17.3.1
Transition State Models for Proline-Catalyzed Reactions

The proposed transition state models assume the participation of enamine intermediate in the critical stereocontrolling bond formation step. The generally used transition states for aldol (**9**), Mannich (**10**), aminoxylation (**11**), α-amination (**12**), and Michael addition (**13**) are summarized in Figure 17.6. A few important advantages arising due to the potential hydrogen bonding between the incoming electrophile and proline carboxylic acid are (i) improved proximity between reactants

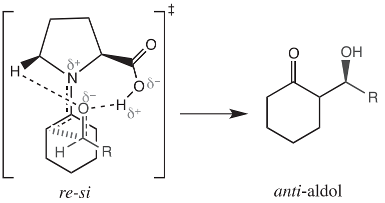


9 **10** **11** **12** **13**

Figure 17.6 Generally employed transition state models for the stereoselectivity-controlling bond formation in proline-catalyzed reactions. Reproduced from Reference [24] with permission from John Wiley & Sons.

as well as probability of reaction, (ii) stabilization of the developing negative charge on the incoming electrophile, and (iii) due to this interaction the preferred approach of the electrophile is proposed to occur from the same face of the carboxylic acid group. Interestingly, in these transition state models the hydrogen bonding and electrostatic interactions are invoked to explain the facial preference exhibited by the nucleophilic proline-enamine. In contrast, if the electrophile approaches from the opposite face of the enamine, with respect to the orientation of the carboxylic acid group, these stabilizing interactions would either be absent or diminishingly lower. It is therefore highly suggestive that transition state stabilization through weak interactions exerts a direct influence in controlling the stereochemical course of the reaction. In fact, the subtle changes in weak interactions, when manifest in tandem, can lead to a cumulative effect that brings about remarkable variations between these reactions.

The enormous success enjoyed by the enamine transition model is due to its applicability to a broader range of substrates and to an equally large number of reactions [25a]. Closer perusal of these transition state models reveals that subtle differences in stabilization play a direct role in bringing about the differential stabilizations of competing diastereomeric transition states [27]. In the case of an intermolecular aldol reaction, the favorable factors that stabilize a transition state in a particular stereochemical mode of addition include, but are not limited to, (i) the hydrogen bonding stabilization offered by the carboxylic acid group to the developing alkoxide ion, (ii) the ability to accommodate the accompanying geometric distortion in the enamine moiety as a new bond develops with the electrophile, (iii) planarity of the nitrogen atom in the incipient iminium ion, and (iv) other weak stabilizing interactions (Scheme 17.5). In most cases, the lowest energy transition state responsible for the major stereoisomer exhibits a nearly ideal balance of these factors while the competing diastereomeric transition state would possess a relatively lower number or reduced efficiency of stabilizing stereoelectronic factors. Gilmour and coworkers have illustrated the importance of noncovalent interactions in controlling the dynamic conformational behavior in modified fluoro derivatives of MacMillan's iminium ions by using NMR spectro-



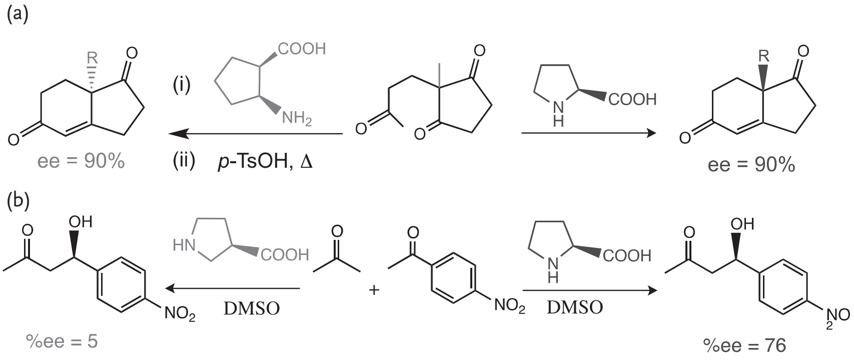
Scheme 17.5 Most preferred transition state for the addition of *anti*-enamine (derived from cyclohexanone and proline) to an aldehyde.

scopic tools. Interesting connections between the geometry of the iminium ion controlled by a phenyl group on the iminium chain and enantioselectivity in the conjugate addition to *N*-methylpyrroles were presented [28].

The success of the Houk–List transition state model for the proline-catalyzed asymmetric intermolecular aldol reaction between cyclohexanone and benzaldehyde (and isopropionaldehyde) has subsequently been extended to various other substrates as well [29]. Houk and coworkers have examined the transition structures using DFT(B3LYP) methods in the alkylation reactions of *N*-methylpyrrole with aldehydes catalyzed by MacMillan's chiral amines [29c]. The Houk–List model has also been successful in rationalizing stereoselectivities in other types of reactions, as given in Figure 17.6. It should be reckoned that the effectiveness of intramolecular weak interactions in the transition states would vary when the incoming electrophile is changed. Besides other factors, a reflection of variations in intramolecular interactions in the transition state can be attributed as one of the reasons for differing stereoselectivities when the same enamine (nucleophile) reacts with different electrophiles. In addition, the role of the pyrrolidine ring conformation in the Hajos–Parrish–Eder–Sauer–Wiechert (HPESW) reaction has been reported by Houk and coworkers [30]. In a combined experimental and DFT(B3LYP) computational study, they evaluated the catalytic ability of *cis*- and *trans*-4,5-methanoproline, a cyclopropane fused proline analogue. While the improved catalytic ability of *cis*-methanoproline is attributed to nearly planar iminium geometry in the transition state, more pyramidalization is noticed in the case of the trans-isomer.

17.3.2
Limitations of Hydrogen-Bonding Guided Transition State Models

The general acceptance of the above-mentioned transition state models has perhaps triggered a series of interesting experiments. For instance, the question of how important the α-disposition of the carboxylic acid group is addressed through examining the catalytic efficiency of β-proline or its analogues. Davies and coworkers employed cispentacin to demonstrate that the HPESW reaction could proceed as good as with α-proline in terms of high enantioselectivity and yield (Scheme 17.6a) [31]. In a similar study, Limbach reported success with aliphatic β-amino acids with ee's up to 83% for the intramolecular aldol reaction while stereoselectivities for the



Scheme 17.6 Comparisons between α and β-proline analogues in an enantioselective aldol reaction.

intermolecular aldol reaction were poor [32]. The intramolecular aldol reaction notably yielded the (*R*) enantiomer, in contrast with α-proline, which offered an (*S*) enantiomer. However, in a related intermolecular aldol reaction between acetone and *p*-nitrobenzaldehyde the β-proline remained ineffective as compared to α-proline [33]. These examples tend to suggest that the transition state models employed toward rationalizing stereoselectivity in α-proline-catalyzed intermolecular aldol reactions may not directly hold good for that involving β-proline analogues. Further studies in this direction are not widely available, perhaps due to the overshadowing dominance of α-proline resulting in relatively less attention being paid to the potential of β-prolines.

As discussed in previous sections, initial experiments to probe the *in situ* existence of enamine intermediate have not been very successful. Furthermore, an increasing number of reports suggest an alternative oxazolidinone species as more likely to be present in solution. Building on these experimental observations, Seebach and Eschenmoser suggested an alternative transition state model (Figure 17.7) [34]. The major difference between the Seebach–Eschenmoser transition state model and the widely used Houk–List model is the face of approach of the electrophile. While the electrophile approaches from the *syn*-face (defined with respect to the orientation of the carboxylic acid group) in the Houk–List model (Figure 17.7a), an *anti*-face addition is suggested in the Seebach–Eschenmoser model (Figure 17.7b). The second key difference is the active species involved in the stereocontrolling transition state. In the Seebach–Eschenmoser model an oxazolidinone intermediate is generated by attack of the carboxylate oxygen on the enamino double bond, which, in turn, leads to the formation of a new bond with the electrophile from the face opposite to the carboxylic acid.

An interesting example was recently reported by Sharma and Sunoj, who demonstrated that the stereoselectivity controlling transition in an aldol reaction, as shown in Scheme 17.7, should originate from enamine carboxylic acid intermediate (**17**) instead of from the deprotonated enamine carboxylate (**21**) [35]. This proposal further implies that the *syn*-face addition of enamine to the electrophile

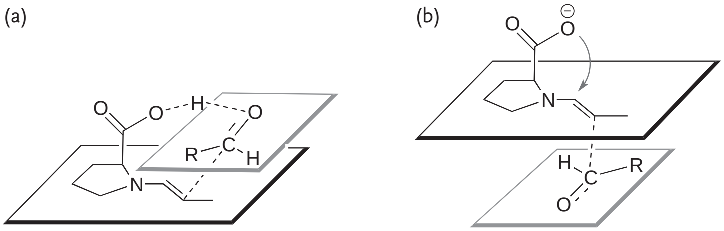
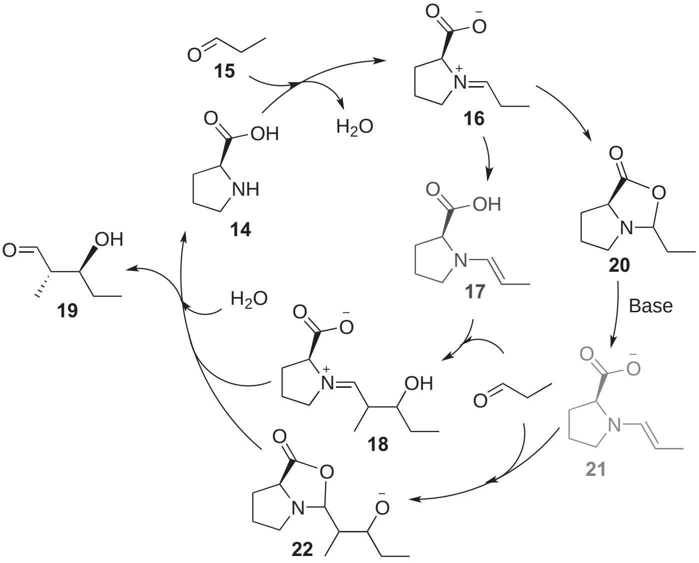


Figure 17.7 (a) *Syn*-face addition in Houk–List models; (b) *anti*-face addition in Seebach–Eschenmoser transition state models.



Scheme 17.7 Key mechanistic possibilities in proline-catalyzed self aldol condensation between two molecules of propanal. Reproduced from Reference [35] with permission from Wiley-VCH Verlag GmbH.

can account for the stereochemical course of the reaction. The computed Gibbs free energy of activation for the stereocontrolling C–C bond formation transition states, as summarized in Figure 17.8, indicates that the enamine carboxylic acid pathway (a) is energetically preferred over the enamine carboxylate pathway (b).

The important aspect of their study relates to the stereochemical mode of addition in the most preferred transition state in (a) and (b). In model-(a), *Re*-face addition of enamine carboxylic acid on the *Re*-face of the aldehyde is the lowest energy addition leading to an enantiomeric excess of about 99% in favor of (2*S*,3*S*) stereoisomer and *anti*-diastereomer as the major product. In model-(b), on the other hand, *anti*-face addition involving the *Si*-*Re* mode respectively between enamine carboxylate and aldehyde is of the lowest energy. This approach predicts

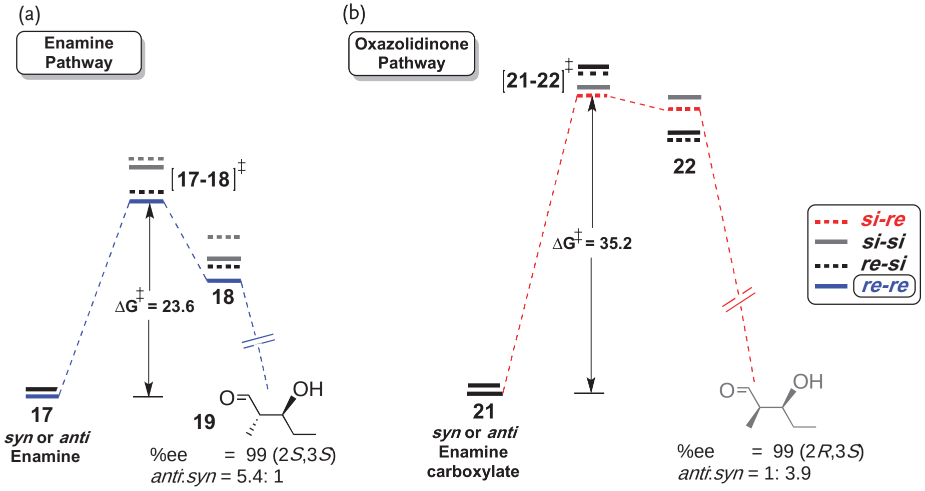
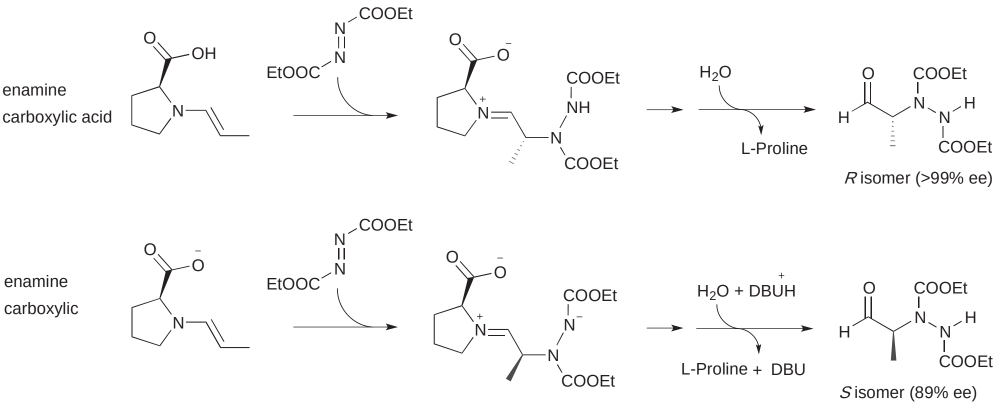


Figure 17.8 Computed Gibbs free energy profiles for the stereoselectivity-controlling C–C bond formation step in (a) enamine pathway involving a Houk–List transition state and (b) enamine carboxylate (oxazolidinone) pathway through Seebach–Eschenmoser transition state models.

a (2*R*,3*S*) configuration besides a *syn*-diastereomeric product, both of which are in contrast with the reported experimental stereochemical outcome of the reaction.

In a closely related study, Sharma and Sunoj examined the validity of transition state models based on *syn*-face and *anti*-face additions under base free as well as basic conditions in a proline-catalyzed α-amination reaction (Scheme 17.8) [36]. Mechanistic investigation using the $\text{PCM}_{(\text{CH}_2\text{Cl}_2)}$/mPW1K/6-31+G** computational method revealed that the addition of enamine carboxylic acid to DEAD



Scheme 17.8 Proline-catalyzed α-amination reaction between propanal and DEAD depicting reversal of stereoselectivity in the presence of a base.

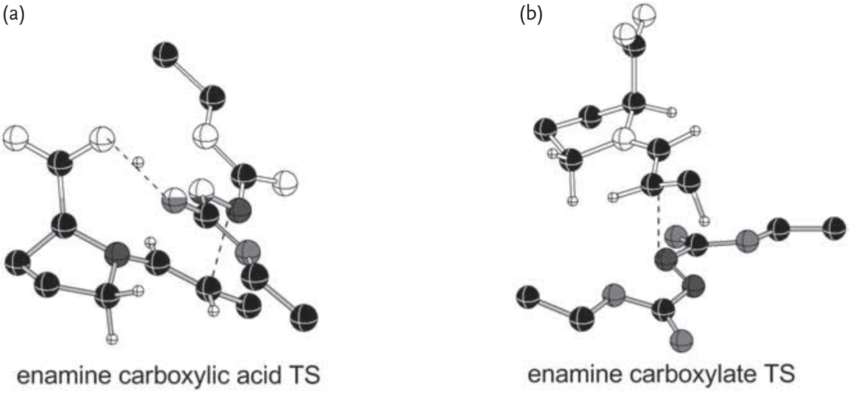


Figure 17.9 Transition state models (a) and (b) employed to rationalize the reversal of stereoselectivity in the presence of DBU in a proline-catalyzed α-amination reaction.

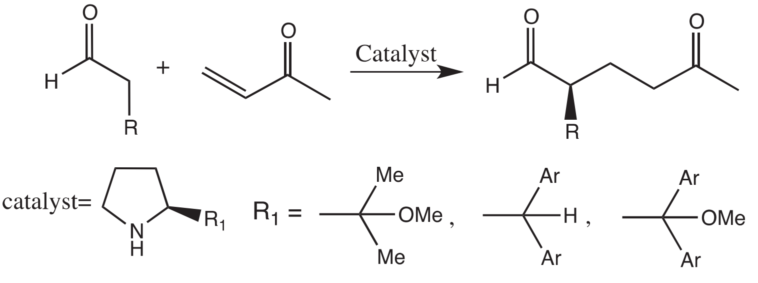
(diethyl azodicarboxylate) yields the correct stereochemical outcome under base-free conditions through the transition state model-(a) as given in Figure 17.9. In this case, the approach of the electrophile is facilitated by hydrogen bonding interaction in the same face of the carboxylic acid group. This model has been found to be successful in reproducing the experimental stereoselectivity reported by Jorgensen and coworkers [37].

It was noticed earlier by Blackmond and Armstrong that inverted product stereochemistry can be obtained in the presence of DBU [38]. The transition state model-(a) alone was found to be incapable of rationalizing the reversal of stereoselectivity. Under basic conditions, it is highly likely that the carboxylic acid group remains deprotonated. The presence of deprotonated carboxylic acid has been corroborated recently [39]. The resulting enamine carboxylate was therefore considered in the vital C–N bond forming step through transition state model-(b). The approach of the electrophile from the *anti*-face of carboxylate is computed to be energetically preferred over the corresponding *syn*-face. The *anti*-face addition would result in formation of a product oxazolidinone described in the previous section. More importantly, the lowest energy transition state predicts formation of the (*S*) enantiomer, in agreement with experimental observations.

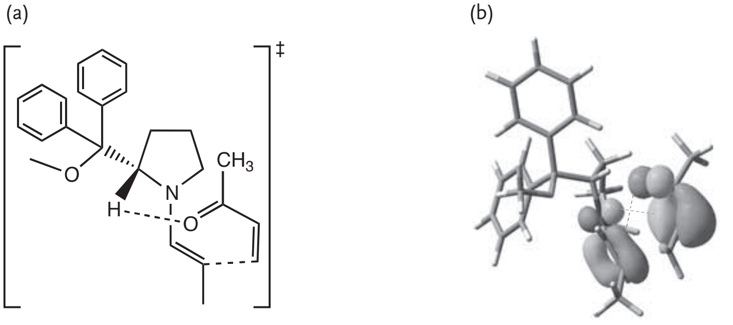
These two examples, of aldol and α-amination, evidently illustrate that a generalized transition state model demands additional refinements, taking the reaction conditions as well into account. While the hydrogen bonding transition state models remained successful for many proline-catalyzed reactions, the applicability of the same to specialized reaction conditions tends to suggest the need for more investigations. Similarly, with a different series of pyrrolidine catalysts devoid of α-carboxylic acid, the need for alternative transition state models to the general hypothesis of *carboxylic acid directed* approach of the electrophile, is more readily evident. For example, one of the most popular pyrrolidine catalysts in use today carries bulkier α-substituents.

With α-substituted pyrrolidine catalysts, there are a few mechanistic issues that deserve to be mentioned. Firstly, the formation of pyrrolidine enamine with the nucleophilic partner could encounter increased steric encumbrance near the amino nitrogen that can result in reduced efficiency. Secondly, alternative mechanisms without the involvement of enamines could also be operating [40]. However, among the limited set of available computational studies on α-substituted pyrrolidines, the enamine pathway has been effective towards rationalizing the stereochemical outcome of the reaction. In most of these, a *steric control* driven transition state model has been invoked wherein the incoming electrophile is guided towards the enamine double bond from the face opposite to that of the bulky α-substituent.

One of the recent examples from our laboratory on stereoselective organocatalytic asymmetric Michael reactions between aldehydes and methyl vinyl ketone (MVK) emphasized the role of several weak interactions in the transition states as responsible for stereoinduction [41]. Three pyrrolidines with α-substituents of varying size have been employed as catalysts for the Michael addition reaction as shown in Scheme 17.9. Several weak interactions, as shown in Figure 17.10, have been proposed to influence the extent of stereoselectivity in this reaction. A balance between the destabilizing steric interactions between MVK and α-pyrrolidine substituents and other weak stabilizing interactions such as the hydrogen-bonding as well as secondary orbital interactions is suggested to hold the key to the stereoselectivity. In particular, a stabilizing hydrogen bonding between the developing alkoxide of the MVK moiety and pyrrolidine αC–H has been identified (Figure 17.10a). More importantly, these weak interactions are found to depend on the nature of the α-substituents. For instance, a substituent bearing a -OMe group can participate in hydrogen bonding stabilization more effectively than a diarylmethyl substituent. An interesting secondary orbital interaction between the enamine and MVK moieties in the C–C bond forming transition state (Figure 17.10b) is found to be important in offering the vital differential stabilization between competing diastereomeric transition states. These secondary orbital interactions can be manifest only within a limited range of relative dihedral angle positions between the reacting substrates. However, in comparison to an aldol reaction, the possible range of dihedral angles that can be spanned between enamine and the electrophilic MVK is much higher in a Michael reaction. This



Scheme 17.9 Chiral pyrrolidine catalyzed Michael addition of aldehydes (R = Me or -CH_2Ar) to methyl vinyl ketone.



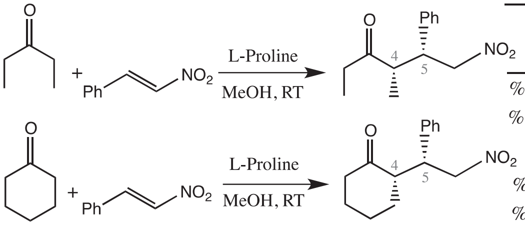
Weak interactions

Secondary orbital interaction

Figure 17.10 Weak interactions in the lowest energy transition state responsible for the stereoselectivity in α-pyrrolidine catalyzed Michael addition between 3-phenylpropanal and methyl vinyl ketone. Reproduced from Reference [41]. with permission American Chemical Society.

additional freedom can also lead to lowering of the stereoselectivity in Michael additions by partially allowing approach of the electrophile even from the hindered face of the pyrrolidine enamine. In the Michael reaction, only the electrophilic carbon needs to position itself with respect to the approaching nucleophile, opening up a larger range of relative geometric possibilities for the approach between the nucleophile and the electrophile.

For the Michael addition between 3-pentanone and nitrostyrene a report by Patil and Sunoj points out a key limitation of the standard enamine derived transition state model when a polar protic reaction medium is employed (Scheme 17.10) [42]. The unassisted transition state inclusive of continuum solvent effects failed to predict the correct stereochemical outcome of the reaction as compared to the experimental observations. The predicted lowest energy transition state has been identified as leading to an incorrect configuration of the newly formed chiral centers as well as the wrong diastereomer. Further refinements to the transition state models were carried out with inclusion of explicit solvent molecules in view of the fact that the reaction being modeled has been conducted in methanol as the solvent. After examining several microsolvated transition states with varying



	Expt.	Computed TS Model-1	TS Model-2
%de	88, *syn*	65, *anti*	64, *syn*
%ee	76,(4*S*,5*R*)	99,(4*S*,5*S*)	90,(4*S*,5*R*)
%de	94, *syn*	85, *anti*	68, *syn*
%ee	57,(4*S*,5*R*)	99,(4*S*,5*S*)	46,(4*S*,5*R*)

Scheme 17.10 Comparison of experimental and DFT(PCM$_{(MeOH)}$/B3LYP/6-311G**//B3LYP/6-31G*) predicted stereochemical outcomes in proline-catalyzed asymmetric Michael addition.

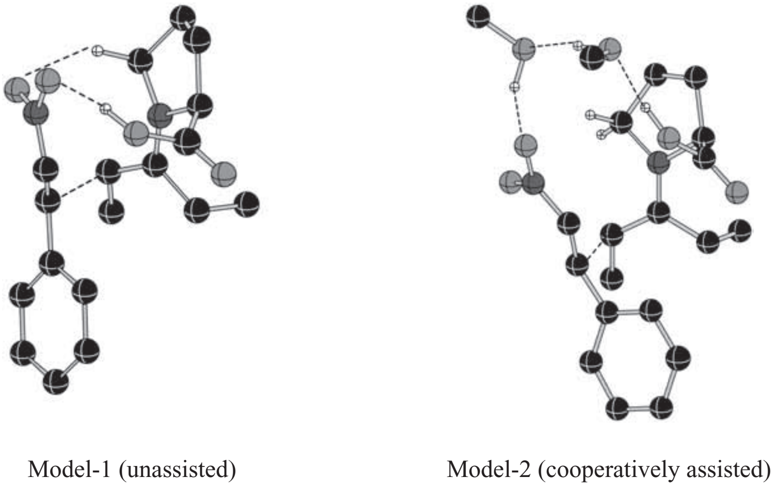


Figure 17.11 Transition state models with and without explicit methanol molecules at the B3LYP/6-31G* level of theory.

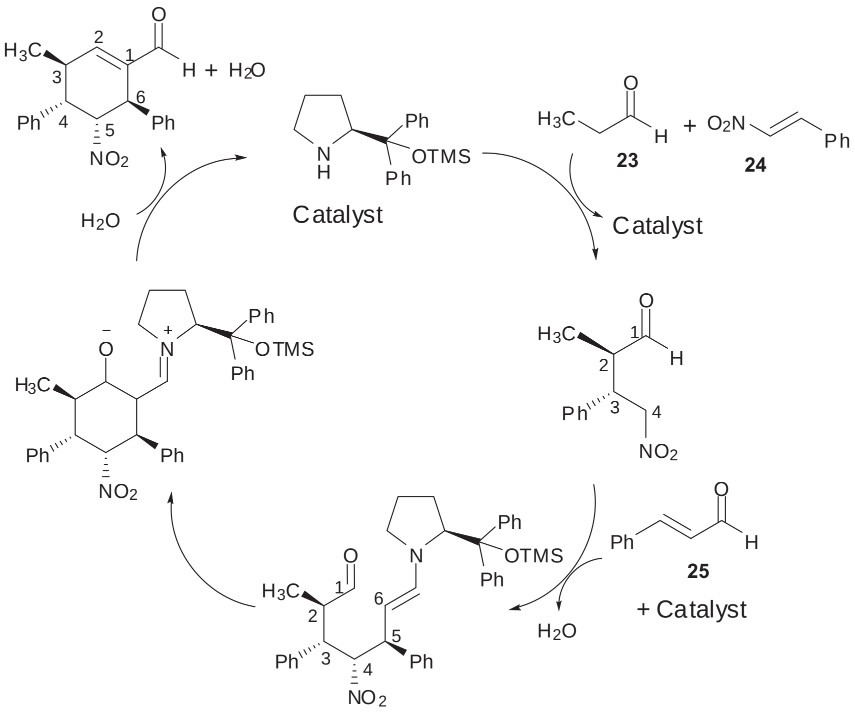
number as well as sites of attachment of the explicit methanol molecules in the stereocontrolling C–C bond forming step, correct predictions on the enantio- and diastereoselectivities could be obtained.

The cooperative hydrogen-bonding interaction between the nitro group and the carboxylic acid, as shown in Figure 17.11, is found to be important to be able to arrive at the right model for the stereocontrolling transition state. When compared to an aldol reaction, the extent of charge dispersion in a Michael acceptor is expected to be different. While a more defined localized tetrahedral alkoxide ion is formed in an aldol reaction, a relatively delocalized charge distribution over an extended π-framework characterizes the Michael addition transition states. Such molecular attributes can lead to noticeable differences in the way a Michael reaction transition state would respond to the surrounding solvent medium, particularly through the specific interactions with the solvent molecules.

In a very recent study on the Michael addition of aldehydes and ketones to nitrostyrene, Wong and coworkers proposed an alternative transition state model wherein the approach of the electrophile is from the face opposite to that of the carboxylic acid group [43]. Of the different transition state structures examined, the one without the hydrogen bonding interaction between the carboxylic acid group of proline and the substrate (nitrostyrene) is proposed as a suitable model for rationalizing the stereochemical outcome.

17.4
Mechanism and Stereoselectivity in Organocatalytic Cascade Reactions

The efforts to put together the advantages of different organocatalytic protocols have given rise to the invention of cascade as well as one-pot reactions [44]. Any mechanistic studies are naturally expected to be more complex owing to the larger number of possible combinations between various reactants. Shinisha and Sunoj have reported a detailed computational study using the DFT(B3LYP/6-31G*) level of theory on a triple cascade reaction between an aldehyde (**23**), an electron-deficient olefin (**24**), and an α,β-unsaturated aldehyde (**25**) (Scheme 17.11) [45]. The initial experimental report due to Enders and coworkers demonstrated that diarylprolinol trimethylsilyl ether can generate four contiguous stereocenters with a high degree of stereoselectivity in favor of (3*S*,4*S*,5*R*,6*R*)-2-methyl-5-nitro-4,6-diphenylcyclohex-1-ene carbaldehyde as the final product [46]. More importantly, mechanistic investigations aimed to establish the reasons behind the isolation of only two epimers out of 16 possible stereoisomers.



Scheme 17.11 Proposed catalytic cycle for the diphenylprolinol trimethylsilyl ether catalyzed triple cascade reaction for the generation of tetrasubstituted cyclohexene carbaldehyde. Reproduced from Reference [45] with permission from the Royal Society of Chemistry.

The combination of reactants in the sequence shown in Scheme 17.11 has been considered in detail. There are two key stereocontrolling C–C bond formation steps in the sequence. The first is the addition of the enamine derived from propanal (**23**) to nitrostyrene (**24**) responsible for the first two stereocenters, while the second step involves the addition of the anion generated from the nitroalkane intermediate to enal **25**. The transition states for stereochemically distinct modes

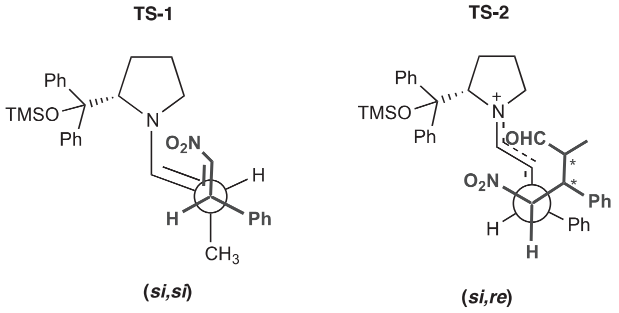
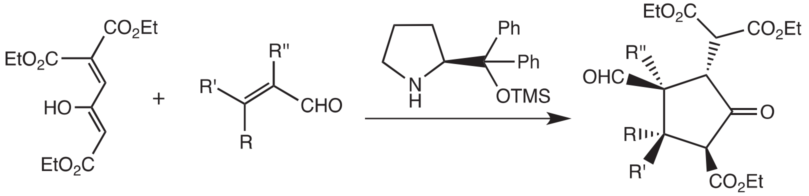


Figure 17.12 Stereocontrolling transition states responsible for the generation of four contiguous stereocenters.

of additions between the reactants in each of these steps have been computed. The most preferred mode in the first step is found to involve addition of the *Si*-face of (*E*)-*anti*-enamine to the *Si*-face of nitro-styrene, represented as TS-1 in Figure 17.12. This addition would lead to a product nitroalkane with a (2*R*,3*S*) configuration at the newly formed stereocenters. The energetically lowest energy iminium ion generated between the catalyst and enal C is found to exhibit (*E,s-trans,E*) stereochemistry. In the next vital step, the most preferred mode involves the addition of the *Si*-face of nitroalkane anion to the *Re*-face of the iminium ion as shown in TS-2. In the last step, intramolecular aldol cyclization would furnish the product. A comparison between the transition state geometries revealed that the extent of stereoselectivity is governed by the steric shielding offered by the bulky α-substituent to one face of the iminium/enamine intermediates in the stereocontrolling bond formation step. Electrostatic stabilizations as well as a network of weak hydrogen bonding interactions involving methylene hydrogens of the pyrrolidine ring, oxygens of the nitro group, and aryl hydrogens are identified as contributing to the differential stabilization of diastereomeric transition states.

Along similar lines, a DFT computational study on a double Michael cascade reaction, as shown in Scheme 17.12, has been reported by Chen and coworkers [47]. They proposed an iminium–enamine catalytic cycle wherein the stereochemistry is controlled by the catalyst backbone, which participates in C–H···O hydrogen bonding interaction with the substrates.



Scheme 17.12 Diarylprolinol silyl ether catalyzed cascade reaction leading to four contiguous stereocenters.

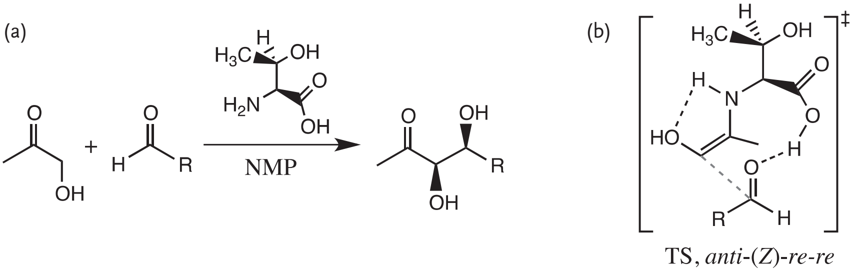


Figure 17.13 Threonine catalyzed aldol reaction (a) and the corresponding stereocontrolling transition states (b) obtained through DFT studies. (R = *p*-nitrophenyl).

17.4.1
Stereoselectivity in Other Amino Acid Catalyzed Reactions

Although the number of successful applications of primary amino acids in stereoselective organocatalysis is far fewer than for the secondary amine, a few interesting examples are worth pointing out. The diversity of primary amino acids in aldol and Mannich reactions has been reviewed recently [48]. Several primary amino acids, such as alanine, valine, tryptophan, and threonine have been used as organocatalysts. For instance, Barbas and coworkers have demonstrated the use of a L-threonine catalyzed protocol towards the synthesis of *syn*-1,2-diols through direct aldol reaction between α-hydroxyketones and *para*-nitrobenzaldehyde (Figure 17.13) [49].

Fu and coworkers employed DFT(B3LYP/6-31+G**) computations to locate the transition states for the stereocontrolling C–C bond formation of the above-mentioned reaction [50]. As with proline-catalyzed reactions, the transition state models are suggested to heavily rely on hydrogen bonding between the carboxylic acid group and the incoming electrophile. However, a few interesting differences are identified such as the preferred geometry of threonine–enamine. The presence of a favorable hydrogen bonding interaction between the NH and the OH groups, as shown in Figure 17.13, renders improved stability to *anti*-(*Z*)-enamine geometry as preferred over *anti*-(*E*)-enamine. The most preferred transition state therefore involves the addition of the *Re* face of *anti*-(*Z*)-enamine to the *Re*-face of aldehyde, leading to *syn*-1,2-diol as the major diastereomer.

Houk and coworker have examined the stereoselectivity in a series of amino acids in an intramolecular aldol reaction using the DFT(B3LYP) computational tool [51]. They attributed increased conformational flexibility in the stereoselective bond forming transition state as the origin of the lower enantiomeric excess noted with acyclic primary amino acids. Himo, Cordova, and coworkers have used density functional theory computations to examine the stereocontrolling transition states for the (*S*)-alanine catalyzed intermolecular aldol reaction between cyclohexanone and *para*-nitrobenzaldehyde [52]. In a very recent study, Houk, Mahrwald, and coworkers compared the transition states of an asymmetric aldol reaction

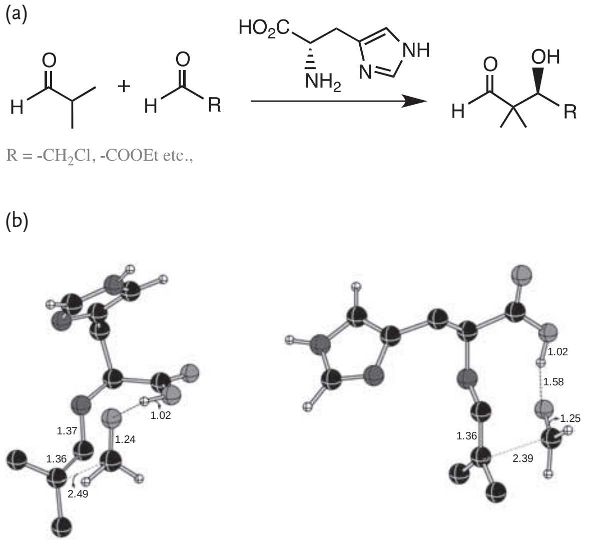


Figure 17.14 (*S*)-Histidine catalyzed aldol reaction (a), and stereocontrolling transition states for a representative example (a).

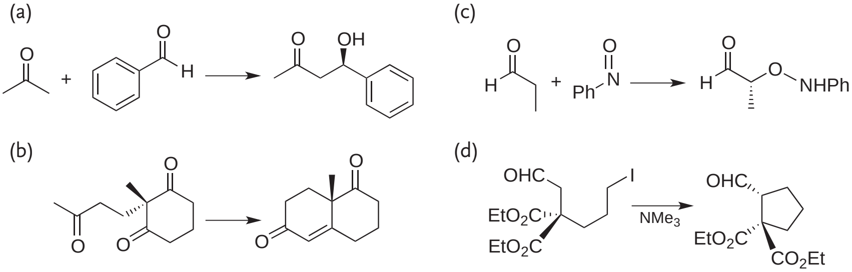
catalyzed by histidine as well as tryptophan using DFT(M06-2X/6-31+G**) computations [53]. The lowest energy transition state and its diastereomeric counterpart, as shown in Figure 17.14, reveal a hydrogen bond directed approach between the enamine and the incoming electrophile. In the stereocontrolling transition states across the different substrates examined, the imidazolium and carboxylic acid groups were identified as offering vital hydrogen bonding stabilization in the aldol addition step.

17.5
Rational Design of Catalysts

The key to partnership between theory and experiments in organocatalysis rests with the ability of the former to precisely identify the transition states responsible for stereoselectivity. In the following section, some prototypical organocatalytic reactions are presented wherein the computational methods were impressively successful. There are more exciting applications wherein a priori predictions were attempted ahead of experimental verification. As a prelude to *in silico* catalyst design, a comparison between the computational predictions of the stereochemical outcome and the experimentally observed enantiomeric excess values for a representative set of proline-catalyzed reactions (Scheme 17.13) is compiled in Table 17.1.

Table 17.1 Comparison between computed and experimental enantiomeric excess values.

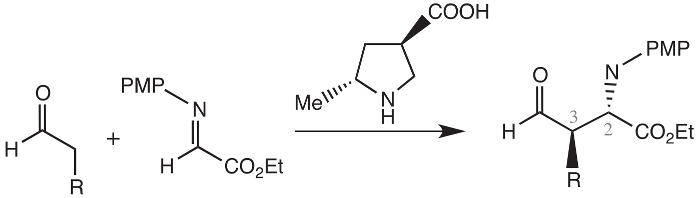
Reaction	Catalyst	Computed ee (%)	Experimental ee (%)	Method	Reference
(a) Aldol	Proline	75	76	B3LYP	[45]
(a) Aldol	5,5-Dimethylthiazolidine-carboxylic acid	80–92	89	B3LYP	[25a]
(b) Aldol	Proline	99	95	B3LYP	[51]
(c) Aminoxylation	Proline	97	99	B3LYP	[51]
(d) Nucleophilic substitution	Proline	66	68	B3LYP	[54]



Scheme 17.13 Selected examples of proline-catalyzed reactions where the enantiomeric excess has been predicted by using DFT computations with enamines in the stereoselective bond formation.

The molecular-level insights gathered through transition state modeling for a variety of organocatalytic reactions have also been employed to design novel catalysts [55]. In a recent commentary on the role of computational tools in the design of small-molecule catalysts Houk proposed that the predictive role of computations in asymmetric reaction should be regarded as the first line of attack in catalyst design [56]. There are a few critical issues that warrant some discussion at this juncture. Knowledge of the reaction mechanism of the given reaction is important and can be considered as the starting point for *in silico* catalyst design. In particular, the precise transition state for the stereocontrolling step should be identified and the stereoelectronic interactions carefully analyzed. Such insights could offer valuable guidelines for rational modifications toward new catalysts. One should further take into account the order of difficulty in realizing the designed catalysts from a synthetic standpoint. The beginning of success in such attempts rests pragmatically with how the designed catalysts are received by experimental chemists. Improved synergism and trust between theoretical and experimental communities appears to be the way forward toward exploiting the predictive capabilities of modern computational chemistry tools.

In this section, a set of select examples are illustrated wherein the transition state models offered valuable clues for rational modifications to existing catalysts. In one of the earliest examples of computational design of organocatalysts, Houk, Tanaka, Barbas, and coworkers demonstrated how effectively one can modify the catalyst to provide the *anti*-diastereomer with high enantiomeric excess in a Mannich reaction [57]. The proposed theme, as shown in Scheme 17.14, is of high contemporary significance as most of the prevailing methods provide access to the *syn*-diastereomer, including that using proline as the catalyst.



Scheme 17.14 Example of *anti*-selective Mannich reaction between *N*-*p*-methoxyphenyl (PMP) protected imine catalyzed by 5-methyl-3-pyrrolidine carboxylic acid.

The authors first examined how the parent proline imparts stereoselectivity using transition state models as shown in Figure 17.15. It was identified that in the most preferred mode of addition in the case of proline the *Re*-face of (*E*)-enamine in *s-trans* conformation adds to the *Si*-face of aldimine leading to a *syn*-diastereomer. The optimal distance for the proton transfer from the carboxylic acid to the aldimine nitrogen is particularly significant as it is regarded as one of the key stereocontrolling factors that induce facial preference for the incoming electrophile. Now, two clever modifications have been incorporated in an attempt to reverse the preferred face offered by the enamine to the incoming electrophile.

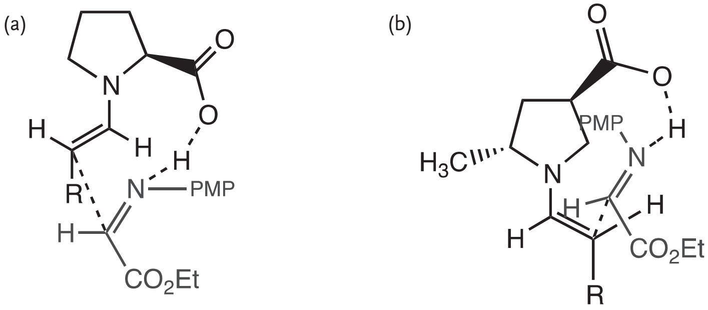
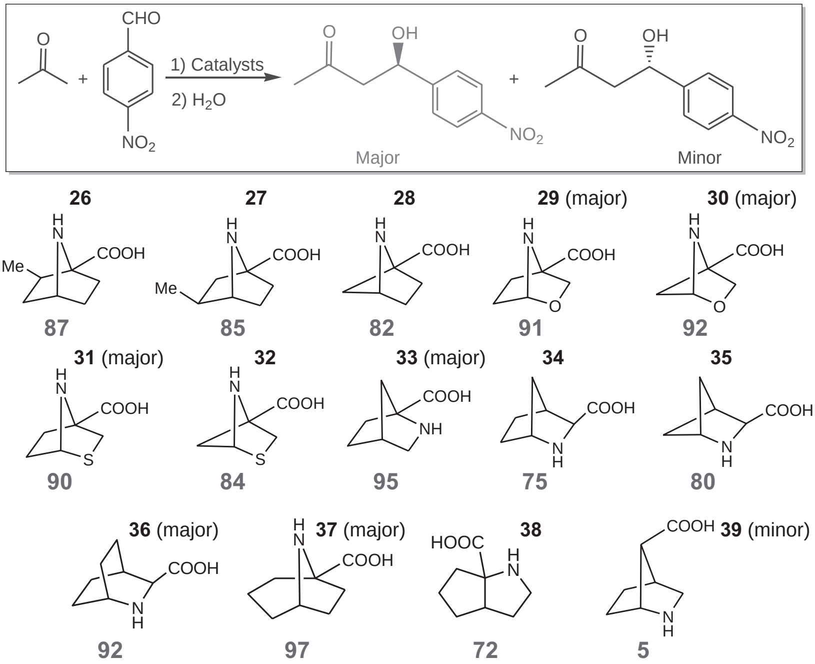


Figure 17.15 Transition states for (a) *syn*-selective Mannich reaction for unmodified proline and (b) *anti*-selective Mannich reaction for 5-methyl-3-pyrrolidinecarboxylic acid.

First, the carboxylic acid group is moved farther to the third position and an additional *trans* methyl group is introduced at the fifth position. While the later substituent would steer the enamine conformation to an *s-trans* arrangement, the carboxylic acid can still participate in effective proton transfer as shown in Figure 17.15b. The relative energies of transition states indicated 95 : 5 *anti* : *syn* diastereoselectivity and about 98% enantiomeric excess for the (2*S*,3*R*)-Mannich product. Subsequent experimental verification of these predictions yielded near quantitative agreements for the extent of both enantio- and diastereoselectivities in favor of *anti*-Mannich product.

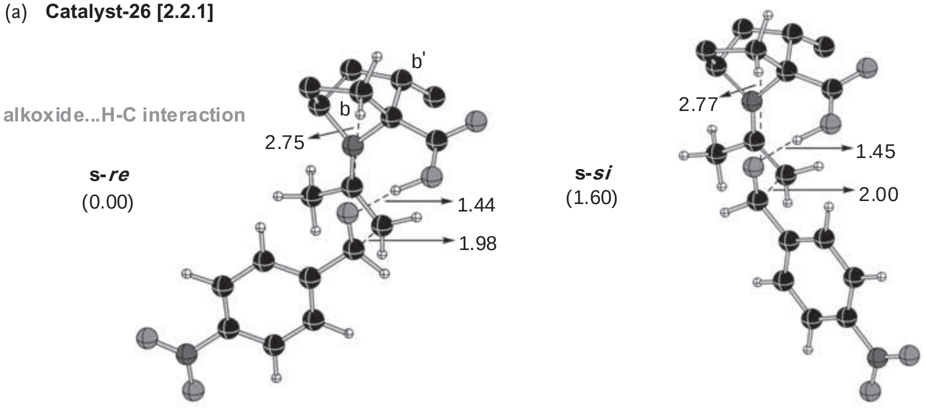
Another prediction on the modification of pyrrolidine carboxylic acid as organocatalyst for an asymmetric aldol reaction between acetone and *para*-nitrobenzaldehyde has been put forward by Shinisha and Sunoj (Scheme 17.15) [58]. On the basis of DFT(B3LYP/6-311+G**) computations, a series of bicyclic analogues of α-amino acids were proposed for their potential to bring about improvements in enantiomeric excess as compared to the parent proline. The suggested bicyclic α-amino acids consisting of an envelope conformer of pyrrolidine that differ in terms of the group that remains out-of-plane. In addition, one β-amino acid was also compared with the corresponding α-series. These catalysts (**26–39**) along with the computed enantiomeric excess values are provided in Scheme 17.15.



Scheme 17.15 Bicyclic pyrrolidine catalysts and the corresponding enantiomeric excess computed using transition state modeling. The higher and lower ee's are indicated.

Rational modifications of the catalyst structure have been carried out to increase the energy separation between the vital diastereomeric transition states. Figure 17.16 provides a representative set of optimized geometries of the transition states so as to illustrate these modifications. Examination of the weak interactions in the most preferred mode of addition, involving *syn* enamine addition to the *Re* face of benzaldehyde, indicates a weak interaction between the developing charge on the alkoxide oxygen and one of the pyrrolidine methylene groups (2.75 Å). While the interaction is expected to be relatively weaker, the same interaction in the diastereomeric transition state exhibits a moderate difference. Fine-tuning of this interaction has subsequently been carried out by increasing the acidity of the methylenic hydrogens by introducing heteroatoms such as oxygen, as in catalysts **29** and **30**. Two interesting predictions emerged through these modifications to the catalyst framework. Firstly, the alkoxide interaction became stronger and led to increased differential stabilization that translates into higher enantiomeric excess. The [2.2.1] as well as [2.1.1] bicyclic systems were found to be more effective in improving

(a) **Catalyst-26 [2.2.1]**



(b) **Catalyst-29 [2.2.1]** (c) **Catalyst-30 [2.1.1]**

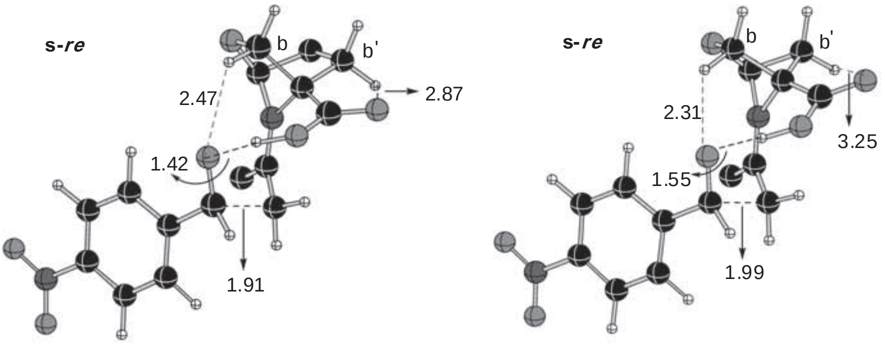
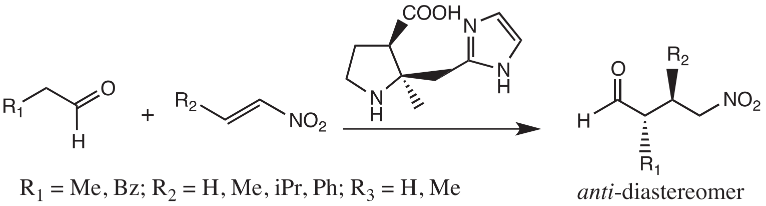


Figure 17.16 B3LYP/6-31G* optimized geometries of (a) two lower energy diastereomeric transition states for catalyst-**26**, and the most preferred modes of additions in the case of (b) catalyst-**29** and (c) catalyst-**30**.

the stereoselectivity above 90%. It is interesting to compare with the experimental as well as predicted ee's for parent proline for the same reaction. These values are 75% and 76%, respectively.

The proposed concept that the conformational restraint imposed on the pyrrolidine framework in the form of bicyclic framework could lead to improved stereoselectivity was experimentally verified by Armstrong and coworkers [33]. Additional experimental verification, particularly on highly selective bicyclic catalysts, would indeed be of interest.

In another recent study, Wong and coworkers have used DFT computations to design a few β-amino acid organocatalysts based on the concept of a catalytic carboxyl/imidazole dyad [59]. The catalysts, as shown in Scheme 17.16, have been predicted to perform well in asymmetric Michael additions between aldehydes and nitroolefins. Mechanistic studies using the DFT(M06/6-31G**) method revealed that the enamine derived from the aldehyde and substrate remains in the (*E*)-configuration. The relative energies of the stereocontrolling transition states indicated high enantio- as well as diastereoselectivities in the Michael addition reaction. Although the predictions appear to be encouraging, experimental validation of these results is as yet unknown.



R_1 = Me, Bz; R_2 = H, Me, iPr, Ph; R_3 = H, Me

Scheme 17.16 Michael addition between aldehydes and nitroolefins catalyzed by designed β-amino acid leading to *anti*-diastereomeric products.

On the basis of some of these attempts to design novel organocatalysts using computational methods as well as similar endeavors in other domains of chemical catalysis, an optimistic outlook on the predictive power of computational methods appears reasonable. With the advent of increasingly faster computing facilities worldwide, the inclusion of environmental and other factors that are likely to influence the course of the reaction into the predictive protocol would become progressively easier. While *in silico* design potential is more widely employed in drug discovery programs toward identifying lead compounds, a parallel effort by chemists is perhaps lagging behind.

17.6
Summary and Conclusions

An overview of molecular insights into the mechanism of several organocatalyzed reactions has been the focus of this chapter. The contents are expected to gel well with an overwhelmingly diverse experimental literature in the field, as presented in other chapters. It has therefore been our aim to begin with details of the energetics of formation of the key intermediates under different reaction conditions. The stereoselective bond formation step has been described in more detail by presenting various transition state models obtained through computational investigations. A comparative account of important transition state models and their success as well as the key limitations in the case of proline catalysis has been delineated. The consensus between computational predictions and the corresponding experimental observations on the stereochemical outcome of several secondary amine catalyzed reactions has generally been impressive. In this context, a section on rational catalyst design using computational tools has also been included. In conclusion, this chapter offers a series of take-home messages on the mechanism of enamine catalysis and stereoselective bond formation transition states and their significance in potential catalyst design.

Acknowledgments

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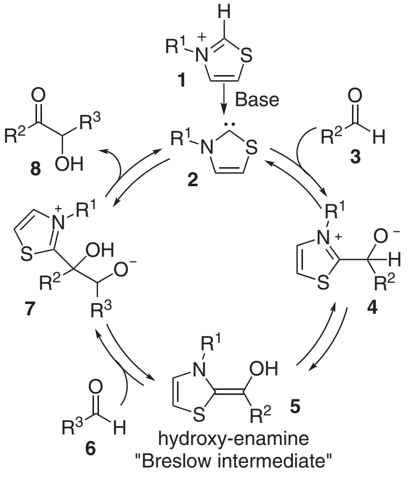
18
Carbene Catalysts

Karen Thai, Eduardo Sánchez-Larios, and Michel Gravel

18.1
Introduction

Long before the catalytic activity of N-heterocyclic carbenes (NHCs) was discovered, Wöhler and Liebig reported the first benzoin reaction in 1832 [1]. Although their reaction was catalyzed by cyanide, it would lay the synthetic and mechanistic foundations for the umpolung reactions that constitute a cornerstone of NHC organocatalysis. Over a century later, Ukai and coworkers disclosed the catalytic activity of thiazolium salts in the benzoin reaction under basic conditions [2]. This observation gained added significance when it was found by Mizuhara and coworkers that the thiazolium moiety of the coenzyme thiamin is essential for its biocatalytic activity [3]. Breslow proposed a common mechanistic rationale for these observations in 1958 that is still widely accepted today [4]. According to this mechanism for the benzoin reaction (Scheme 18.1), the thiazolium salt **1** is first



Scheme 18.1 Mechanism of the benzoin reaction, according to Breslow.

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deprotonated to form an NHC (**2**). The *in situ* generated carbene then attacks an aldehyde (**3**), leading to the formation of a hydroxy-enamine or "Breslow intermediate" (**5**) following a formal 1,2-proton shift. This acyl anion equivalent attacks a second aldehyde (**6**), leading to the benzoin product (**8**) following a proton transfer and regeneration of the carbene catalyst. Although there has been no unambiguous identification of a Breslow intermediate to date [5], other intermediates and related species have been characterized [6].

Through the presumed intermediacy of Breslow intermediates, several other reactions have been developed featuring an inversion of reactivity for the aldehyde or *umpolung* [7, 8]. Other reactions in which the NHC plays the role of a nucleophilic or basic catalyst have also been reported recently. Although each type of catalysis is conceptually distinct, some generalities can be drawn from their common use of NHC catalysts.

The most commonly employed precatalysts can be divided into four families: thiazolium (**9**), triazolium (**10**), imidazolium (**11**), and imidazolinium (**12**) salts (Figure 18.1), each with unique properties and reactivity profile.

The azolium salts' acidity is determined not only by the type of heterocycle but also by the nature of the ring substituents (Figure 18.2) [9]. Despite the importance of the salts' acidities, the pK_a of some of the most commonly used azolium salts has not been reported. Inferences can nevertheless be made in some cases. For instance, *N*-C_6F_5 triazolium **17** was found to be completely deprotonated by one equivalent of 1,8-diazabicycloundec-7-ene (DBU) in CD_2Cl_2 whereas *N*-mesityl triazolium **18** was only partially deprotonated [10]. Of note, the use of very weak bases can be sufficient or even beneficial in some cases, despite the presence of only small amounts of active carbene catalyst in the reaction mixture [10, 11].

Another aspect of practical importance in NHC-catalyzed reactions is the stability and air sensitivity of the carbenes and reaction intermediates. Whereas decom-

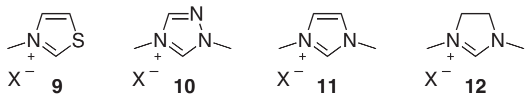


Figure 18.1 Families of common azolium salts.

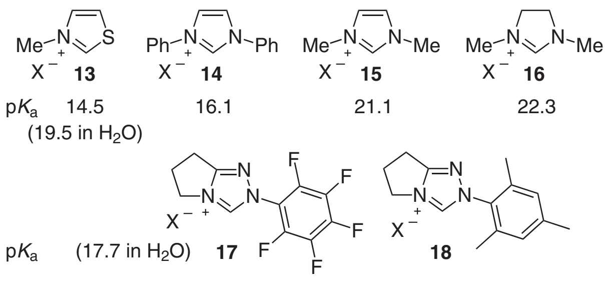


Figure 18.2 pK_a values in DMSO for some azolium salts.

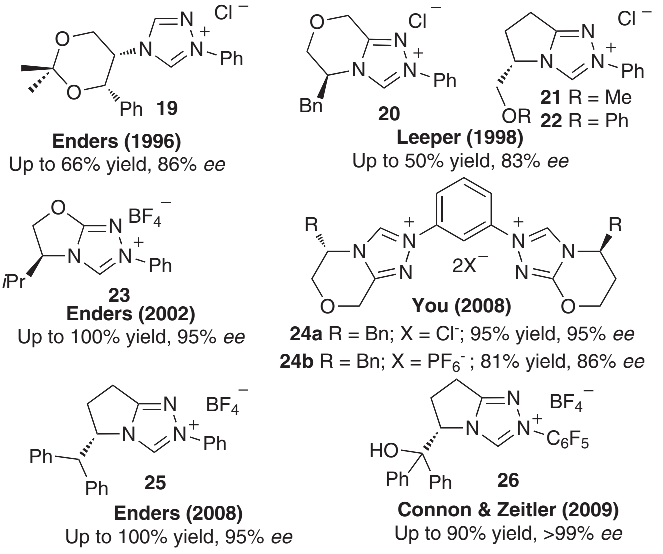
position or alternative reaction pathways were found to be available in the presence of adventitious oxygen or water [12] other reactions were found to be quite tolerant and could be performed open to air [13]. In addition, and importantly, NHCs need not be stable to be effective catalysts. For instance, the relatively unstable thiazolium- and triazolium-derived NHCs have found widespread applications in reactions of acyl anion equivalents while the more stable imidazolium- and imidazolinium-derived NHCs generally display inferior reactivity.

18.2
Reactions of Acyl Anion Equivalents

18.2.1
Benzoin Reaction

18.2.1.1 Homo-Benzoin Reaction

Initial investigations into enantioselective benzoin reactions were performed using chiral thiazolium salts as NHC precursors. Although pioneering efforts from Sheehan and coworker only delivered benzoin products with low enantioselectivity [14], ee values of up to 57% could be achieved through variation of the thiazolium salt structure and reaction conditions [15]. The breakthrough in achieving high enantioselectivity and high yields was made possible through the development of chiral triazolium salts, as pioneered by Enders and coworkers (Figure 18.3) [16].



19
Enders (1996)
Up to 66% yield, 86% *ee*
20
21 R = Me
22 R = Ph
Leeper (1998)
Up to 50% yield, 83% *ee*
23
Enders (2002)
Up to 100% yield, 95% *ee*
You (2008)
24a R = Bn; X = Cl⁻; 95% yield, 95% *ee*
24b R = Bn; X = PF₆⁻; 81% yield, 86% *ee*
25
Enders (2008)
Up to 100% yield, 95% *ee*
26
Connon & Zeitler (2009)
Up to 90% yield, >99% *ee*

Figure 18.3 Chiral triazolium salts for the benzoin reaction.

It has been argued that the increased steric bulk near the carbene center is responsible for the higher selectivities generally observed when using triazolium salts *vis-à-vis* thiazolium salts [17], and detailed computations have been performed on various systems [18]. Knight and Leeper introduced fused bicyclic triazolium salts **20–22** derived from naturally occurring amino acids [19]. The increased conformational rigidity of these catalysts has made them quite popular and numerous fused bicyclic triazolium salts have been developed since. Through these developments, excellent yields and enantioselectivities have been achieved for the homobenzoin reaction of aromatic aldehydes (up to >99% ee) [20]. Whereas good enantioselectivity can also be achieved in the case of heteroaromatic aldehydes (up to 88% ee), the homo-coupling of aliphatic aldehydes has only proceeded with high enantioselectivity in a few cases when using a thiamine-dependent enzyme [21]. Interestingly, You and coworkers noticed a significant difference in rate and enantioselectivity in the benzoin reaction of benzaldehyde when varying the counterion of a bis-triazolium salt (**24a** versus **24b**) [20b].

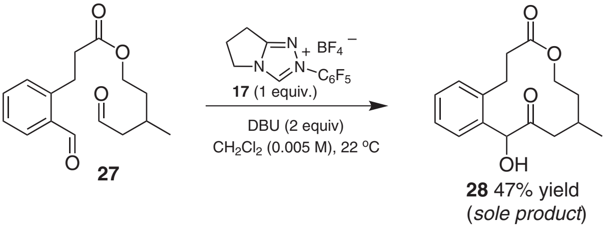
18.2.1.2 **Cross-Benzoin Reaction**

The chemo- and enantioselective cross-coupling of two different aldehydes via a benzoin reaction remains a significant challenge. Four different benzoin products can be formed (two homo- and two cross-benzoin products), each as two possible enantiomers. The challenge is compounded by the commonly observed reversibility of the reaction.

Several reports have described cross-benzoin reactions involving formaldehyde as the acceptor to obtain achiral hydroxymethyl ketones [22]. Although the chemoselectivity was shown to be kinetically-controlled in some cases, the factors behind this selectivity remain unclear.

In 2002, Müller and coworkers disclosed cross-benzoin reactions between *o*-unsubstituted and *o*-Cl or *o*-F benzaldehyde derivatives catalyzed by thiamin diphosphate-dependent enzymes [23]. In these highly chemo- and enantioselective reactions, the less sterically hindered *o*-unsubstituted benzaldehyde selectively forms the Breslow intermediate, which then attacks the more electrophilic *o*-halo benzaldehyde. Similar chemoselectivity was later shown by Glorius and coworkers using achiral *N*-aryl or *N*-alkyl thiazolium salts [24].

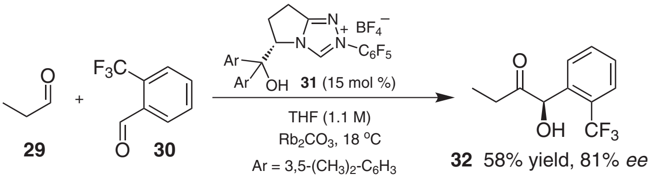
Mennen and Miller reported the macrocyclization of dialdehydes to obtain the cross-benzoin products in low yields but high chemoselectivity using an *N*-C_6F_5 triazolium precatalyst (Scheme 18.2) [25]. The chemoselective formation of **28** was



Scheme 18.2 Cross-benzoin macrocyclization of α,ω-dialdehydes, according to Miller and coworkers.

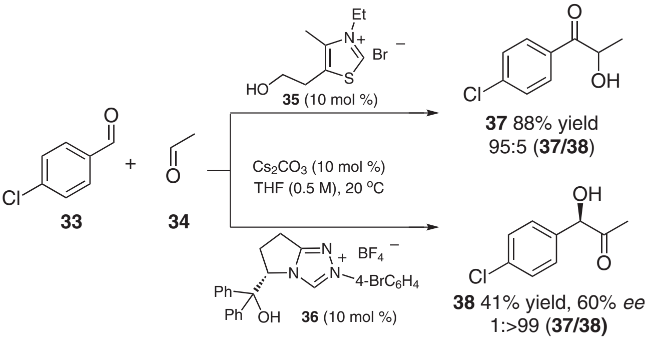
determined to be under kinetic control, with the aliphatic aldehyde acting as the acyl anion equivalent. A chemoselective intermolecular cross-benzoin reaction was also achieved between *o*-tolualdehyde and *n*-hexanal under similar conditions, again showing a preference for the benzylic alcohol product. In contrast, the use of benzaldehyde and *n*-hexanal resulted in a mixture of benzoin products, showing the importance of the *o*-substituent under these conditions.

In 2011, Connon, Zeitler, and coworkers reported detailed studies on intermolecular cross-benzoin reactions using triazolium and thiazolium salts [26]. These systematic studies clearly showed the intricate interplay of various factors influencing the outcome of cross-benzoin reactions. In line with the results of Miller and coworkers, the use of *o*-substituted benzaldehydes resulted in selective formation of benzylic alcohol products using either triazolium or thiazolium salts. When using *o*-unsubstituted benzaldehydes, the same chemoselectivity could be achieved with an α-branched aliphatic aldehyde and an *N*-C_6F_5 triazolium catalyst. Crossover experiments showed the reaction to be under kinetic control in many cases. When using chiral catalyst **31**, good chemo- and enantioselectivity was achieved in the reaction between *o*-trifluoromethylbenzaldehyde (**30**) and propanal (**29**) (Scheme 18.3).



Scheme 18.3 Enantioselective cross-benzoin reaction, according to Connon, Zeitler, and coworkers.

Yang and coworkers reported chemoselective cross-benzoin reactions between *o*-unsubstituted benzaldehydes and an excess (10 equiv.) of acetaldehyde (Scheme 18.4) [27]. Either cross-benzoin product **37** or **38** could be obtained selectively by employing a thiazolium or triazolium salt, respectively. The chemoselective

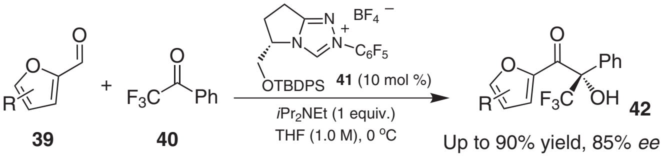


Scheme 18.4 Chemoselective cross-benzoin reactions, according to Yang and coworkers.

formation of the cross-benzoin product **38** from an *o*-unsubstituted benzaldehyde (**33**) is in contrast with the results of Miller and coworkers and Connon, Zeitler, and coworkers, and the large excess of acetaldehyde used may explain the observed selectivity. The authors proposed that the difference in steric bulk between catalysts **35** and **36** may explain the opposite chemoselectivity, but equilibration via a retro-benzoin reaction when using thiazolium salts cannot be ruled out.

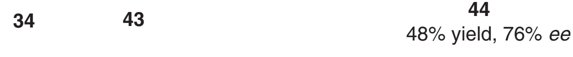
The enantioselective intramolecular cross-coupling of aldehydes and ketones to access cyclic α-hydroxy ketones has also been demonstrated. Issues of chemoselectivity are largely avoided in these cases, and the benzoin reaction can be achieved in a highly efficient and enantioselective manner (up to 93% yield and 99% ee) [28]. The usefulness of the intramolecular cross-benzoin reaction was elegantly illustrated in two separate cyclizations for the synthesis of seragakinone A, an antifungal and antibacterial natural product [29].

Enders and coworkers reported moderate to good enantioselectivity for the coupling of heteroaromatic aldehydes and highly electrophilic trifluoromethyl ketones in the presence of chiral triazolium salt **41** (Scheme 18.5) [30]. It was shown that a reversible homo-benzoin reaction takes place initially, followed by an irreversible cross-benzoin reaction involving the ketone (**40**).



Scheme 18.5 Cross-benzoin reaction of trifluoromethyl ketones, according to Enders and coworkers.

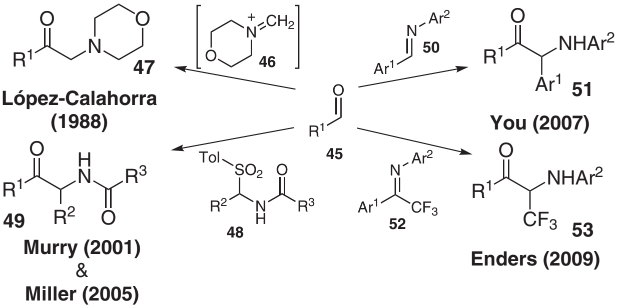
Connon, Zeitler, and coworkers showed α-ketoesters to be competent reaction partners when using *N*-C_6F_5 triazolium salt **17** [31]. Even aliphatic α-ketoesters could serve as substrates while avoiding possible competing aldol pathways. The enantioselective version of the reaction proved challenging, and cross-benzoin product **44** could be obtained in only moderate yield and enantioselectivity (Scheme 18.6). Intermolecular formal cross-benzoin reactions using pyruvate as an aldehyde equivalent were also shown to be possible, using a thiamine-dependent enzyme, with broad substrate scope [32].



Scheme 18.6 Cross-benzoin reaction of α-ketoesters, according to Connon, Zeitler, and coworkers.

18.2.1.3 Aza-Benzoin Reaction

Aza-benzoin reactions have been achieved through the coupling of aldehydes and aldimines [33] or ketimines [34], providing access to α-amino ketones (Scheme 18.7). Despite a first report by López-Calahorra dating back to 1988, this area of investigation can still be considered to be in its infancy. So far, only the use of thiazolium precatalysts has been reported for this reaction, which may in part explain the dearth of enantioselective versions [35]. In a noteworthy exception, a thiazolium-containing tripeptide developed by Miller and coworkers could induce good enantioselectivity (up to 87% ee) in the coupling of aromatic aldehydes with *N*-acyl imines [33c]. While a reversible homo-benzoin reaction was observed in some of these cases, the formation of products derived from an aza-Breslow intermediate was not reported [6g].



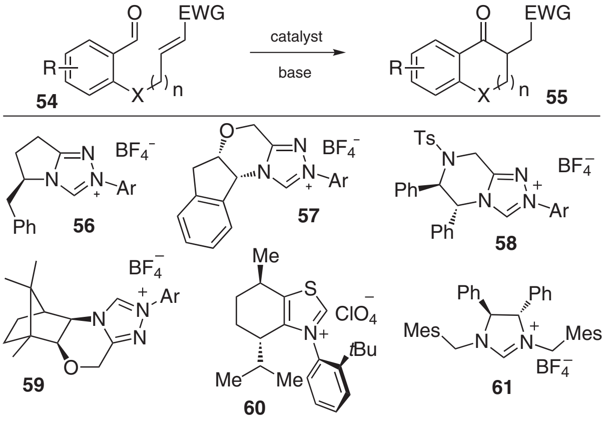
Scheme 18.7 Aza-benzoin reactions to access α-amino ketones.

18.2.2
Stetter Reaction

In the early 1970s, Stetter and Schreckenberg discovered the conjugate addition of aldehydes onto Michael acceptors employing cyanide [36] or thiazolium salts as catalysts [37, 38].

18.2.2.1 Intramolecular Stetter Reactions

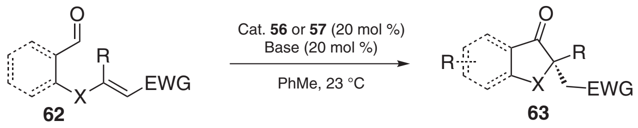
The Stetter reaction received little attention until the disclosure of an intramolecular version by Ciganek in 1995 (Scheme 18.8, X = O, n = 0–1, EWG = CO_2R) [39]. The following year, Enders *et al.* reported the first enantioselective intramolecular Stetter reaction [40], achieving up to 74% ee with moderate to good yields using triazolium catalyst **19** (X = O, n = 1, EWG = CO_2R). Following these pioneering reports, Rovis and coworkers developed conformationally restricted L-phenylalanine- and aminoindanol-derived triazolium salts (**56** and **57**) and demonstrated their efficiency in a series of landmark studies. Various linkers (X = O, S, NR, CH_2) and acceptors [EWG = CO_2R, COR, $CONR_2$, COSR, CN, $P(O)R_2$, $P(O)OR_2$] could be used to obtain chromanones and derivatives in high yields (up to 97%) and high ee's (up to 97%) [12c, 41]. Subsequent mechanistic investigations revealed the first



Scheme 18.8 Intramolecular Stetter reaction to access chromanones and derivatives.

irreversible step to be the proton transfer towards the formation of the Breslow intermediate [42]. The faster reaction when using a heteroatom-containing tether can be explained by the ethereal oxygen acting as a proton transfer agent in this symmetry forbidden 1,2-proton shift. Other research groups have developed a variety of catalysts and conditions for the intramolecular Stetter reaction. You and coworkers achieved high enantioselectivities (up to 97% ee) using diphenyl ethylenediamine-derived (**58**) and camphor-derived (**59**) triazolium salts [43]. Bach and coworkers and Miller and coworkers have reported axially chiral (**60**) and tripeptide-derived thiazolium salts, respectively [44]. Tomioka and coworkers have shown that seldom-used chiral imidazolinium salts (**61**) can also act as catalysts for the intramolecular Stetter reaction [45]. So far, thiazolium and imidazolinium salts have delivered the products in lower enantioselectivity than triazolium-derived catalysts.

Aliphatic substrates displaying increased conformational freedom proved more challenging. Although the formation of five-membered rings proceeded uneventfully, the construction of six-membered rings required more electrophilic acceptor moieties such as alkylidene malonates. Both aliphatic and aromatic aldehydes tethered to a β,β-disubstituted acceptor (**62**) efficiently provided five-membered rings (**63**) featuring a new tetrasubstituted stereocenter with up to 99% ee (Scheme 18.9) [46].



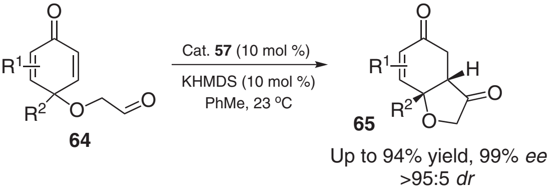
X = CH_2, O, S, SO_2, NAc
EWG = CO_2R, COR

Up to 94% yield
Up to 99% *ee*

Scheme 18.9 Intramolecular Stetter reaction of β,β-disubstituted acceptors, according to Rovis and coworkers.

Xu and coworkers have found that acetic acid added as a co-catalyst helps to stabilize the active NHC catalyst derived from a triazolium salt and sodium acetate [11c]. As a consequence, an efficient Stetter reaction could be performed with a catalytic loading as low as 2.5 mol%.

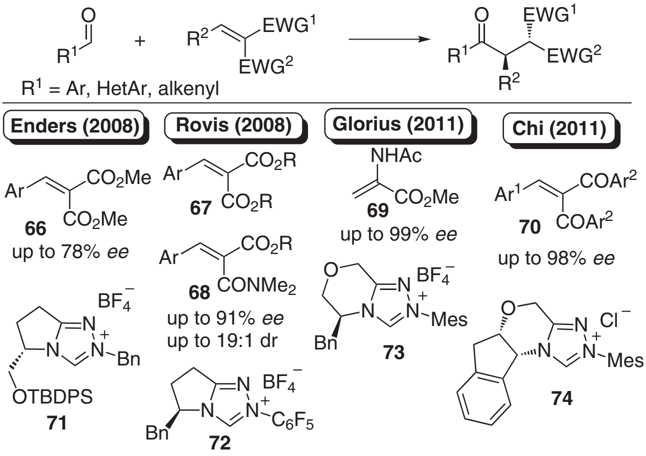
An interesting variation on the intramolecular Stetter reaction was disclosed in 2006 by Rovis and coworkers [47]. Both *O*- and *C*-substituted cyclohexadienones could be desymmetrized using a chiral *N*-anisyl-triazolium salt in high diastereo- and enantioselectivity (up to >99% ee) (Scheme 18.10). All-carbon quaternary and up to three contiguous stereocenters could be formed in this process, with the α-alkoxy group apparently not involved in redox events (see below).



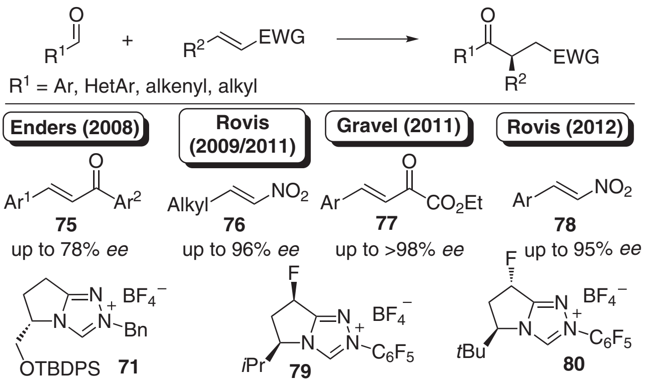
Scheme 18.10 Desymmetrization of cyclohexadienones, according to Rovis and coworkers.

18.2.2.2 Intermolecular Stetter Reactions

In 2008, Enders and coworkers reported the first high-yielding enantioselective intermolecular Stetter reactions employing chalcones and arylidene-malonates as acceptors and *N*-Bn triazolium salt **71** as precatalyst (Schemes 18.11 and 18.12) [48]. The use of an *N*-benzyl instead of the usual *N*-aryl substituent on the triazolium ring was crucial for the activity and selectivity of the catalyst. Rovis *et al.* subsequently disclosed a highly enantioselective Stetter reaction of alkylidene-



Scheme 18.11 Enantioselective intermolecular Stetter reactions of doubly activated acceptors.



Scheme 18.12 Enantioselective intermolecular Stetter reactions of mono-activated acceptors.

malonates **67** employing glyoxamides as highly reactive aldehyde partners [49]. In 2009, the same group reported high enantioselectivities in the reaction between β-alkyl nitroalkenes **76** and heteroaromatic aldehydes [50]. The preparation of novel backbone-fluorinated triazolium salt **79** proved to be instrumental to the success of this methodology. The efficiency of the catalyst was initially ascribed to conformational effects, and later to an electrostatic interaction between the C–F dipole and the developing charge on the nitronate in the transition state [51]. Gravel and coworkers subsequently found the same catalyst (**79**) to be optimal when using highly electrophilic β,γ-unsaturated α-ketoesters (**77**) [52]. Interestingly, Rovis and coworkers found the *trans*-fluorinated catalyst **80** to be both more reactive and more selective than the *cis* isomer in the reaction between aliphatic aldehydes and nitrostyrene derivatives (**78**) [53]. Although the method is poorly tolerant to branching on the aldehyde, it constitutes the first example of an effective intermolecular enantioselective Stetter reaction using aliphatic aldehydes. A stabilizing electrostatic interaction between the aryl substituent and the fluorine atom in the transition state was shown computationally to be a key factor in this transformation. The use of enals as aldehyde partners is complicated by homoenolate reactivity (see below) and by their poor acyl anion reactivity, not to mention their potential role as acceptors. Rovis and coworkers successfully used them in reactions with nitroalkenes (**76**) by adding catechol as a proton shuttle to facilitate the turnover-limiting proton transfer leading to the Breslow intermediate [54]. Alternatively, Chi and coworkers showed the use of enals by employing the very electrophilic α-benzoyl-chalcones **70** as acceptors [55].

In an elegant variant of the Stetter reaction, Glorius and coworkers reported the preparation of α-amino acid derivatives via a diastereoselective protonation of the enolate intermediate generated from α-acylamido β-unsubstituted acrylates (**69**) [56].

Although these recent developments show that various substrates can be used to obtain Stetter products in high yields and enantiomeric ratios, the required combination of aldehyde, acceptor, catalyst, and reaction conditions is both critical and difficult to anticipate. The enantioselective Stetter reaction between aliphatic

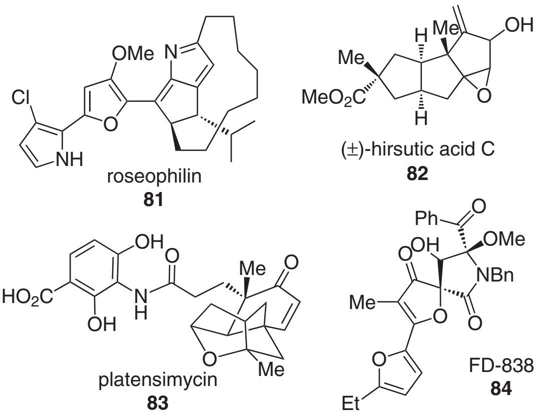


Figure 18.4 Natural products synthesized using a Stetter reaction.

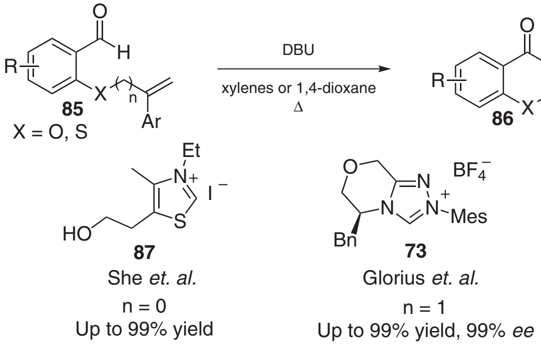
aldehydes and β-alkyl unsaturated ketones, esters, or amides is conspicuously absent from the above discussion. As of 2012, these synthetically useful substrate combinations remain as unanswered challenges.

18.2.2.3 Application of Stetter Reactions to Natural Product Synthesis

Owing to its long-standing limitations, the Stetter reaction has been utilized in a limited number of syntheses (Figure 18.4). β-Unsubstituted acceptors have been used *en route* to *cis*-jasmone and dihydrojasmone [57], roseophilin (**81**) [58], (±)-*trans*-sabinene hydrate [59], monomorine I [60], and haloperidol [61], while a doubly activated Michael acceptor was used to access an intermediate in the synthesis of atorvastatin [62]. Less reactive β-substituted acceptors could be used intramolecularly in the syntheses of (±)-hirsutic acid C (**82**) [63], (±)-platensimycin (**83**) [64], and polycyclic ether arrays [65], as well as in the enantioselective formation of a spirocyclic intermediate toward FD-838 (**84**) [66].

18.2.3
Hydroacylation Reactions

A surprising observation was reported in 2006 when She, Pan, and coworkers serendipitously discovered the intramolecular addition of aldehydes to electron-rich enol ethers ($n = 0$) catalyzed by thiazolium salt **87** (Scheme 18.13) [67]. Glorius and coworkers later disclosed an intramolecular hydroacylation reaction involving alkynes and alkenes ($n = 1$), including a highly enantioselective version using chiral triazolium catalyst **73** [68]. The intermolecular version was made possible by using highly strained cyclopropenes, providing the addition products in high diastereoselectivity (>20 : 1) and enantioselectivity (up to 96% ee) [69]. The use of electron-rich *N*-aryl substituents on the azolium salts was found to be very beneficial in all cases involving alkenes or alkynes. Both experimental and computational evidence support a concerted hydroacylation step.



Scheme 18.13 Hydroacylation of alkenes.

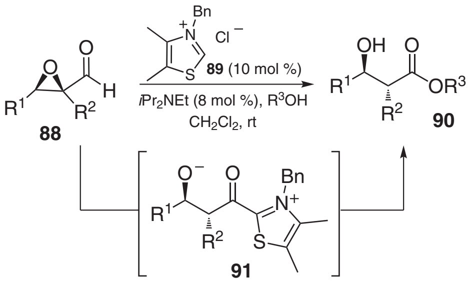
All three types of reactions of acyl anion equivalents presented herein have been used in domino reactions [70]. The typically mild basic conditions required for benzoin, Stetter, and hydroacylation reactions make them amenable to a variety of such applications.

18.3
Extended Umpolung

The realization that productive new pathways could be followed in the presence of reactive functional groups at the α position of aldehydes first came to light in the early part of the twenty-first century. A flurry of new reactions have since been discovered that can be classified under the general term "extended umpolung."

18.3.1
Reactions of α-Reducible Aldehydes

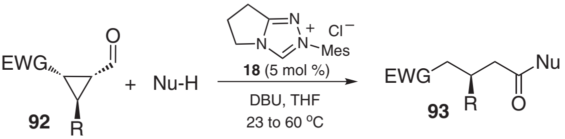
In 2004, the groups of Bode and Rovis independently showed that α-reducible aldehydes could form the corresponding esters in the presence of an alcohol nucleophile and an NHC catalyst. Bode and Chow performed the ring-opening of α,β-epoxy aldehydes **88** to yield β-hydroxy esters **90** in high diastereoselectivity (Scheme 18.14), and showed an analogous example using an α,β-aziridinyl alde-



Scheme 18.14 Redox opening of epoxyaldehyde, according to Bode and coworkers.

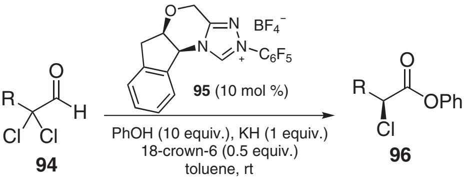
hyde to provide a β-amino ester [71]. This methodology was subsequently used in the synthesis of (+)-davanone [72], largazole, 2-epi-largazole [73], and a fragment of rhizopodin [74].

The concept of ring-opening was extended to strained chiral formyl cyclopropanes **92** bearing an electron-withdrawing group to access chiral β-substituted esters, thioesters, carboxylic acids [75], and amides [76] (Scheme 18.15). The use of an *N*-Mes substituent on the triazolium precatalyst **18** proved greatly beneficial in all cases, in part due to the lower propensity of the corresponding Breslow intermediate to participate as an acyl anion equivalent. The use of imidazole as an additive was found to be necessary in the synthesis of amides, with the formation of an acyl imidazole intermediate playing a key role.



Scheme 18.15 Extension of the redox opening of epoxyaldehyde, according to Bode and coworkers, to strained chiral formyl cyclopropanes.

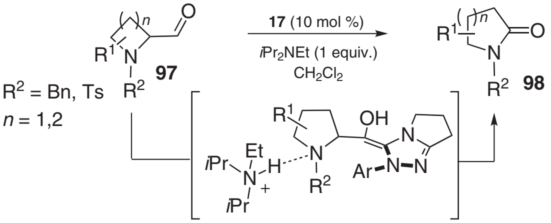
Rovis and coworkers used α-halo aldehydes to generate the formal redox ester products in the presence of an *N*-Ph triazolium salt [77]. This methodology was later extended to the enantioselective formation of phenyl α-chloroesters **96** [78] and α-chloro-carboxylic acids [79] from α,α-dichloro-aldehydes **94** using chiral triazolium salt **95** (Scheme 18.16). Consistent with the simultaneous observations by Bode and coworkers, a nucleophilic co-catalyst was necessary for the formation of amides [80]. An α-chloroamide could be synthesized in good enantioselectivity (80% ee) by the use of chiral triazolium salt **95**.



Scheme 18.16 Redox esterification of α-halo aldehydes, according to Rovis and coworkers.

Following the pioneering work of Bode and Rovis, the *N*-Mes imidazolium catalyzed ring-expansion of formyl β-lactams to access succinimide derivatives was reported by You and coworkers [81], and it was shown to be amenable to kinetic resolution of the β-lactam substrate [82]. Gravel and coworkers then showed the ring expansion of unstrained formyl tetrahydrofurans [12a] and formyl pyrrolidines

(**97**, *n* = 2) [83] catalyzed by a seldom-used imidazolinium salt and *N*-C_6F_5 triazolium salt **17**, respectively. In the latter case, the nature of the base was found to be a determining factor and a co-catalytic hydrogen-bonding role for its conjugate acid was proposed (Scheme 18.17).

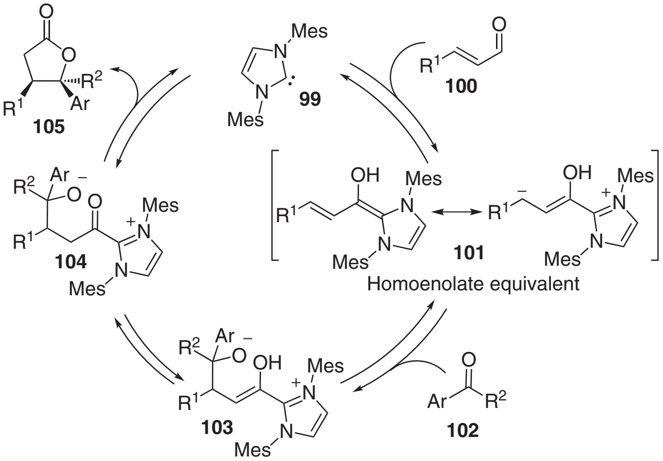


Scheme 18.17 Lactam formation via ring expansion, according to Gravel and coworkers.

18.3.2
Reactions of Enals and Ynals

18.3.2.1 C–C Bond Forming Reactions at the β Position

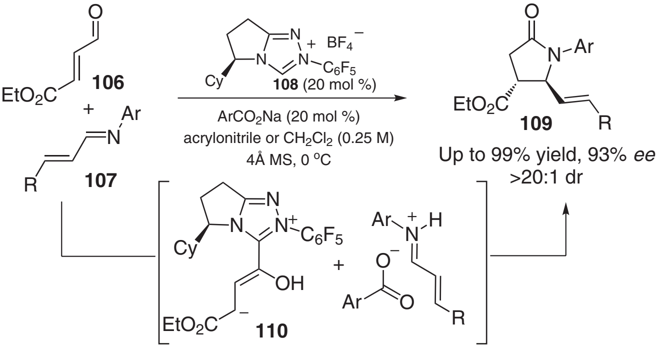
The ability of enals to react as homoenolates [84] in the presence of NHC catalysts was first noted in 2004 independently by the groups of Glorius and Bode [85]. In both cases, the use of sterically-hindered catalyst **99** and a strong base (DBU or Bu^{t}OK) allowed a^3-d^3 umpolung through the extended Breslow intermediate (**101**), thereby attacking an aldehyde electrophile and ultimately forming a γ-lactone diastereoselectively (**105**, R^2 = H) (Scheme 18.18). Whereas two aldehydes can potentially react with the NHC, only homoenolate reactivity is available due to the



Scheme 18.18 Synthesis of lactones via homoenolates, according to Glorius and coworkers and Bode and coworkers.

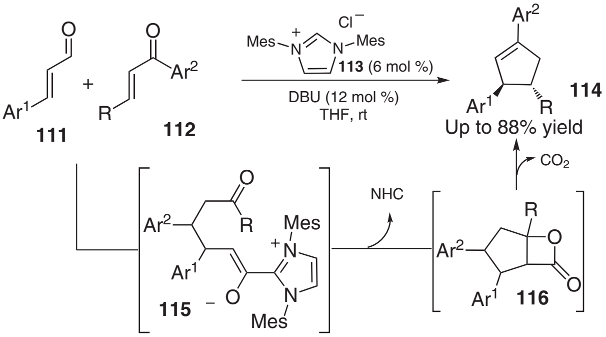
steric hindrance of the catalyst. The chemoselectivity in the subsequent step is controlled by the use of an electron-poor aldehyde to minimize dimerization of the enal. Highly reactive ketones such as trifluoromethyl ketones, α-ketoesters [85a, 86], 1,2-diketones, isatins [87], and tropanone [88] were also shown to be competent electrophiles in this reaction, but the enantioselective formation of lactones using chiral imidazolium or triazolium catalysts has had only limited success [85a, 89, 90], including when a chiral Lewis acid was used [91]. A notable exception arose when a hydroxyl-containing NHC was used by Ye and coworkers to form isatin-derived lactones in a highly diastereo- and enantioselective manner [92]. As with most NHC-catalyzed reactions of enals, the presence of an α- or an additional β-substituent on the enal leads to a sluggish reaction. Nevertheless, the low reactivity of α-methylcinnamaldehydes could be overcome by the use of a less sterically hindered *N,N*-dimethylbenzimidazolium salt [86].

Extension of this work to the diastereoselective synthesis of γ-lactams from *N*-sulfonyl aldimines [93] and ketimines [94] was subsequently reported. Scheidt and coworkers disclosed an enantioselective version (up to 98% ee) from reactive hydrazones in the initial demonstration of cooperative NHC/Lewis acid catalysis using a bulky, chiral triazolium salt and catalytic $Mg(OBu^t)_2$ [95]. Rovis and coworkers synthesized γ-lactams **109** enantioselectively using a chiral *N*-C_6F_5 triazolium salt (Scheme 18.19). A weak carboxylate base was sufficient to partially deprotonate the precatalyst **108** *in situ,* and the carboxylic acid formed could activate the *N*-Ar imine acceptor **107** via protonation [11b]. In all these cases, a fine balance must exist between sufficient electrophilicity *vis-à-vis* the competing enal and reversible addition of the carbene to the imine/hydrazone/iminium or to the Lewis acid.



Scheme 18.19 Synthesis of γ-lactams via homoenolates, according to Rovis and coworkers.

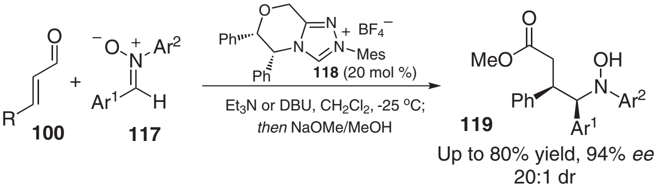
Nair and coworkers showed in 2006 that Michael acceptors (**112**) can also act as electrophiles for achiral imidazolium-derived homoenolates, although the expected cyclopentanone products were not obtained [96]. Instead, *cis*-substituted cyclopentenes **114** resulting from a proton transfer, aldol, β-lactone formation, and decarboxylation sequence were isolated (Scheme 18.20).



Scheme 18.20 Synthesis of cyclopentenes via homoenolates, according to Nair and coworkers.

Bode and coworkers later introduced a highly enantioselective version of this cyclopentene synthesis by using aminoindanol-derived triazolium salt *ent*-**74** [97]. Intriguingly, they also proposed a cross-benzoin/oxy-Cope mechanism for this transformation, which may better explain the diastereoselectivity of the process. Computational studies carried out by Domingo and coworkers favor the conjugate addition pathway initially proposed by the Nair group [98]. In another early demonstration of NHC/Lewis acid co-catalysis, Scheidt and coworkers predominantly obtained the *trans* cyclopentene using 20 mol% $Ti(OPr^i)_4$ and a bulky chiral triazolium salt [91].

In 2008, Scheidt and coworkers showed that addition of *N*-Mes triazolium-derived homoenolates to nitrones **117** could be performed with high enantioselectivity (Scheme 18.21) [99]. The unstable heterocyclic products could be conveniently opened to the corresponding γ-hydroxyamino esters **119** with sodium methoxide.

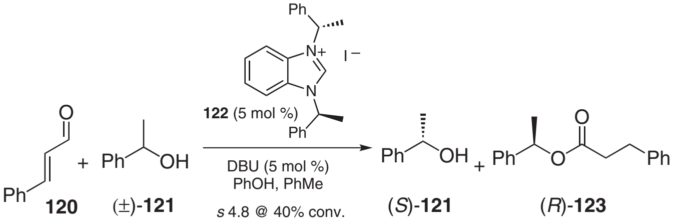


Scheme 18.21 Synthesis of γ-hydroxyamino esters via homoenolates, according to Scheidt and coworkers.

A practical limitation to the use of NHC-derived homoenolates in C–C bond forming reactions is the limited commercial availability and stability of enals. To address this issue, Bode and coworkers have shown that readily synthesized α′-hydroxyenones act as enal surrogates in a wide variety of reactions [100]. However, these surrogates show poor reactivity with common chiral triazolium salts as a consequence of the increased steric bulk.

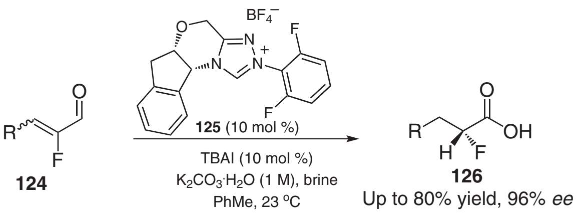
18.3.2.2 β-Protonation of Homoenolates

In early 2005, Scheidt and coworkers reported the possibility of protonating the transient homoenolate intermediate in the presence of phenol and an alcohol to form the corresponding saturated ester [101]. The use of C_2-symmetric benzimidazolium salt **122** allowed the kinetic resolution of chiral secondary alcohol **121** with moderate selectivity ($s = 4.8$) (Scheme 18.22).



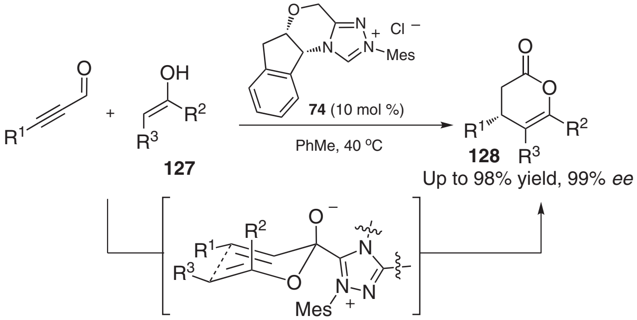
Scheme 18.22 Kinetic resolution of secondary alcohols, according to Scheidt and coworkers.

Sohn and Bode subsequently showed that a combination of *N*-Mes triazolium salt and a weak base such as iPr$_2$NEt allows the reaction to occur under milder conditions [102]. The use of a weak base instead of DBU or Bu^{t}OK allows protonation of the homoenolate by the conjugate acid (or the azolium salt), whereas the hindered triazolium catalyst minimizes acyl anion reactivity and is sufficiently acidic to be deprotonated by an amine. The enantioselective β-protonation of β,β-disubstituted α,β-unsaturated aldehydes with chiral *N*-C$_6$F$_5$ triazolium precatalysts by Scheidt and coworkers led to moderate yields and enantioselectivities (up to 58% yield, 55% ee) [103]. Although enantioselective protonation at the remote β position remains a challenge, Vora and Rovis have shown that α-protonation can be achieved with high enantioselectivity (Scheme 18.23). Enantiomerically-enriched α-fluorinated carboxylic acids **126** can be obtained through the formal redox reaction of α-fluoro-α,β-unsaturated aldehydes **124** [79]. Larger α-substituents dramatically reduce the reactivity of homoenolates and their ability to form α stereogenic centers enantioselectively.



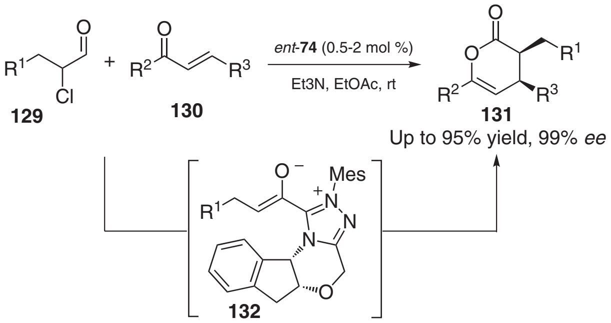
Scheme 18.23 Redox esterification of α-fluoro enals, according to Rovis and coworkers.

Building on the formal redox esterification of ynals discovered by Zeitler [104], the group of Bode showed that the unsaturated acyl azolium intermediate could be trapped by enols to yield dihydropyranones **128** enantioselectively (Scheme 18.24) [11a]. Mechanistically, the enol **127** could perform a 1,4-addition on the acyl azolium followed by a lactonization. Instead, the authors postulate a 1,2-addition/Coates-Claisen rearrangement pathway that is supported by kinetic and computational studies [105]. Another notable finding was a strong counterion dependence on the reaction rate in the absence of added base. The data presented is consistent with the chloride ion in **74** effectively playing the role of base to deprotonate the triazolium cation.



Scheme 18.24 Dihydropyranones formed via Coates-Claisen rearrangement, according to Bode and coworkers.

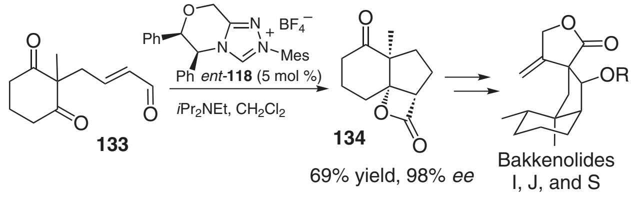
In the absence of a suitable nucleophile, the homoenolate-derived acyl azolium intermediate can undergo deprotonation to generate a nucleophilic azolium enolate. Bode and coworkers showed such enolates to be competent dienophiles in hetero-Diels–Alder reactions with *N*-sulfonyl azadiene partners, providing dihydropyridinone products in very high diastereo- and enantioselectivity [106]. This work was quickly followed up by an analogous hetero-Diels–Alder reaction with oxodienes **130** (Scheme 18.25) [107]. In this case, the enolate intermediates (**132**)



Scheme 18.25 Dihydropyranones formed via a hetero-Diels–Alder reaction, according to Bode and coworkers.

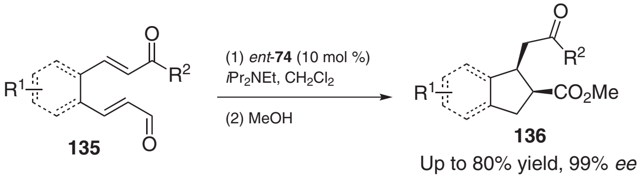
were generated from α-chloroaldehydes **129**. The dihydropyranone products **131** are efficiently obtained in high diastereo- and enantioselectivity using a very low catalyst loading (0.5–2 mol%). Once again, the presence of a bulky *N*-Mes substituent on the chiral triazolium catalyst was necessary to obtain the desired reactivity.

The NHC-generated azolium enolate can also react in a Mannich [11d], Michael [108], or aldol fashion [86], such as in the desymmetrization of 1,3-diketones to access enantiomerically-enriched cyclopentenes following decarboxylation of the β-lactone product [109]. Scheidt and coworkers took advantage of this reaction in the total synthesis of bakkenolides I, J, and S (Scheme 18.26) [110].



Scheme 18.26 Total synthesis of bakkenolides I, J, and S, according to Scheidt and coworkers.

Scheidt and coworkers also showed that enolate intermediates can engage in conjugate additions in the presence of *N*-Mes imidazolium and triazolium catalysts. Indane and cyclopentane products **136** could be synthesized in high yields and excellent enantioselectivity (Scheme 18.27) [111]. However, increasing the tethering chain by one carbon to access six-membered rings resulted in reduced yield and enantioselectivity (52% yield, 62% ee).



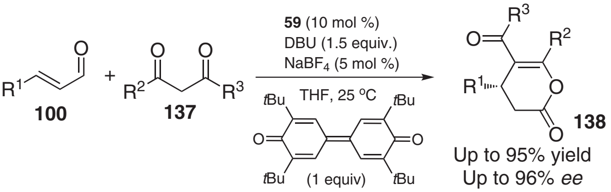
Scheme 18.27 Intramolecular Michael addition, according to Scheidt and coworkers.

Bode and Mahatthananchai have performed thorough studies on the effect of the *N*-Mes group [10]. The observed behavior of catalysts bearing this substituent is mainly the result of their increased steric bulk and electron-donating ability in homoenolate intermediates, particularly with respect to their *N*-C_6F_5 counterparts.

18.3.2.3 **Oxidation of Enals**

Electrophilic acyl azolium species can be generated from the Breslow intermediate in the presence of a mild oxidant such as MnO_2 [112], TEMPO [113], or a quinone

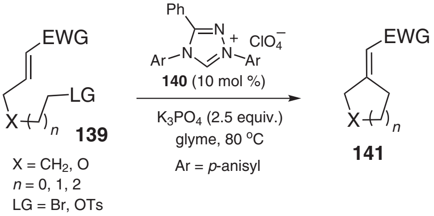
[114]. Taking advantage of this unique mode of activation, the groups of Xiao, You, and Studer independently showed enals to undergo oxidation–Michael addition–acylation sequences to generate dihydropyrones **138** enantioselectively in the presence of 1,3-diketones **137** and *N*-Mes or *N*-C_6F_5 triazolium salts [115]. You and coworkers described an intriguing and very pronounced increase in enantioselectivity when including catalytic amounts of $NaBF_4$, for which they postulate an interaction with the C_6F_5 moiety in the triazolium catalyst (Scheme 18.28).



Scheme 18.28 Dihydropyranones formed via oxidation of enals, according to You and coworkers.

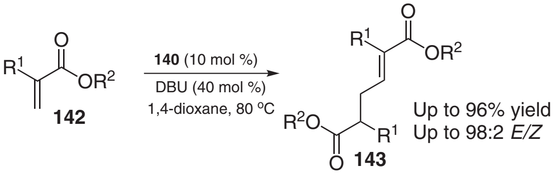
18.4
Umpolung of Activated Olefins

Although the umpolung of aldehydes by NHCs was discovered seven decades ago, only recently did analogous transformations of activated olefins become known. In 2006, Fu and coworkers reported a novel ring-closing reaction involving Michael acceptors tethered to a leaving group via an alkyl chain (**139**), which is equivalent to a metal-free Heck reaction (Scheme 18.29) [116]. Triazolium precatalysts bearing two *N*-anisyl groups (**140**) proved optimal for this transformation, whereas imidazolium and thiazolium salts were much less effective. Acrylate, acrylonitrile, and acrylamide acceptors could be used successfully, as could bromide, chloride, and tosylate leaving groups.



Scheme 18.29 NHC-catalyzed ring closing of Michael acceptors, according to Fu and coworkers.

Five years later, the groups of Matsuoka and Glorius independently reported the tail-to-tail dimerization of α-substituted acrylates **142** (Scheme 18.30) [117]. Again, *N,N′*-diaryl triazolium salts were optimal while none of the other common catalyst families were effective. The dimerization was found to be irreversible and highly

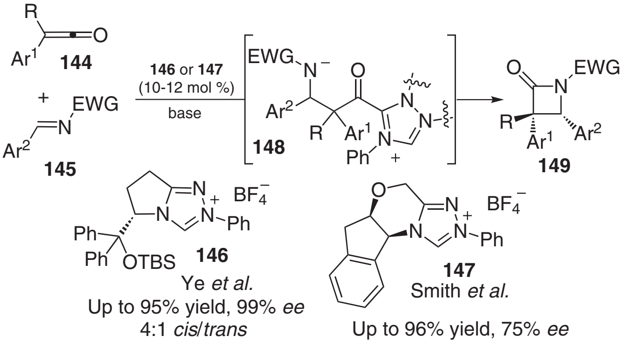


Scheme 18.30 Dimerization of acrylates, according to Matsuoka and coworkers and Glorius and coworkers.

(*E*)-selective under the reaction conditions. The current limitation to β-unsubstituted acrylates restricts the possible enantioselective variants of this reaction. Nevertheless, this type of umpolung constitutes an exciting new direction for the field of NHC organocatalysis.

18.5
Nucleophilic Catalysis

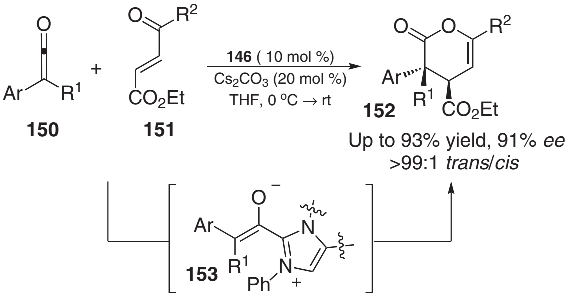
The use of NHCs as transesterification catalysts features among their early applications as nucleophilic catalysts and this area has been reviewed previously [8, 118]. More recently, the formation of nucleophilic azolium enolates via attack of NHCs onto ketenes **144** was reported independently by the groups of Ye and Smith in 2008 [119]. In the presence of *N*-Boc or *N*-Ts aromatic imines **145**, β-lactams **149** were obtained in moderate to high enantioselectivity using chiral *N*-Ph triazolium salts (Scheme 18.31).



Scheme 18.31 Synthesis of β-lactams, according to Ye and coworkers and Smith and coworkers.

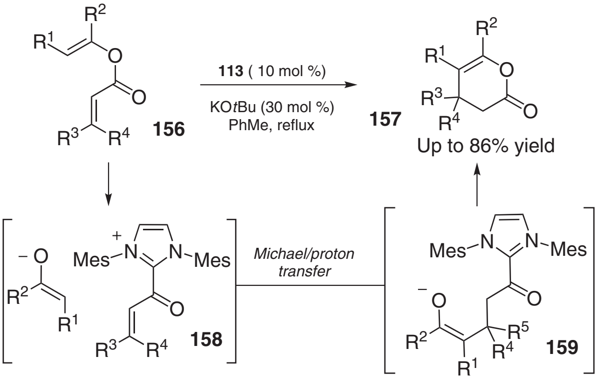
Ye and coworkers have since reported a wide range of cycloadditions using different electrophilic partners, all in the presence of pyroglutamic acid-derived triazolium catalysts [120]. A noteworthy example is represented by the enantioselective formal [4+2] cycloaddition of ketenes with enones **151** to obtain dihydropyranones

152 (Scheme 18.32) [120a]. This case illustrates well the complementarity between this methodology and the alternative generation of azolium enolates (**153**) via proton transfer in homoenolates or formal redox reaction of α-chloroaldehydes (cf. Scheme 18.25). Using ketenes **150** as starting material, dihydropyranones **152** containing a quaternary center could be formed with high enantioselectivity. Interestingly, the required ketenes could be generated *in situ* from the more conveniently handled acid chlorides.



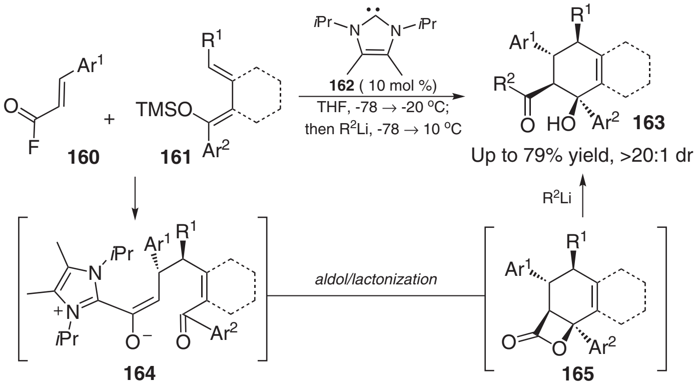
Scheme 18.32 Formal [4+2] cycloaddition of ketenes and enones, according to Ye and coworkers.

In 2009, Lupton and coworkers reported an elegant new method for the formation of dihydropyranones **157** from α,β-unsaturated enol esters **156** in the presence of imidazolium salts (Scheme 18.33) [121]. Acyl substitution by the NHC generates an electrophilic unsaturated acyl azolium species (**158**) analogous to the one generated during the oxidation of enals (see above), which is attacked by the newly released enolate. Extension of this methodology to the reaction of acid fluorides and silyl enol ethers lends credence to the proposed fragmentation-based mechanism, although a concerted Coates-Claisen rearrangement is also possible [105]. A modestly enantioselective version was reported, as well as its application to the synthesis of (–)-7-deoxyloganin [122].



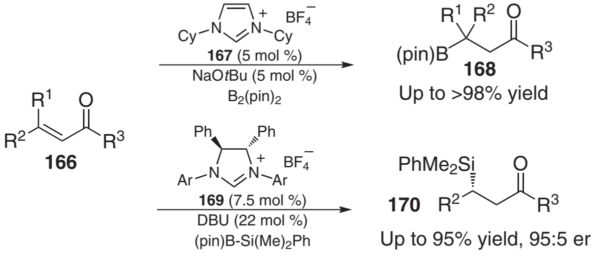
Scheme 18.33 Rearrangement of α,β-unsaturated enol esters, according to Lupton and coworkers.

In a subsequent study by the same group, silyl dienol ethers **161** were shown to intercept the acyl azolium species formed from unsaturated acid fluorides **160** [123]. The 1,3-cyclohexadiene products were initially thought to be formed via a concerted cycloaddition pathway, but later computational experiments suggested a stepwise Michael/aldol pathway [123b]. Maintaining the temperature below −20 °C allowed nucleophilic addition to the β-lactone intermediate **165** rather than decarboxylation, thereby yielding highly substituted cyclohexenes **163** with up to four contiguous stereocenters (Scheme 18.34).



Scheme 18.34 Formal [4+2]/lactonization/addition reaction, according to Lupton and coworkers.

Notwithstanding the extremely rich and diverse reactivity presented above, all the examples presented thus far feature the addition of an NHC catalyst onto an sp^2 carbon. Several reactions have been developed in the last ten years describing the activation of heteroatom σ bonds by NHCs [8c]. The concept can be well illustrated by the recent work of Hoveyda and coworkers, who reported boryl and silyl conjugate additions to α,β-unsaturated carbonyls (Scheme 18.35) [124]. In both cases, addition of the NHC onto a trivalent boron atom activated the B–heteroatom bond. The use of C_2-symmetric imidazolinium salt **169** in the silyl conjugate addition led to β-silyl ketones, esters, and aldehydes in good to high enantioselectivity.



Scheme 18.35 Boryl and silyl conjugate additions, according to Hoveyda and coworkers.

18.6 Conclusion

The use of NHCs as organocatalysts has been the object of tremendous interest, particularly over the last decade. The breakthroughs that have been accomplished with respect to the benzoin and Stetter reactions, as well as the large variety of new reaction types, augur well for the future of this area of study. In view of these advances, the more widespread application of NHC organocatalysis in the realm of synthesis seems possible.

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19
Oxides and Epoxides

Harry J. Milner and Alan Armstrong

Oxidation reactions make up an important class of organocatalyzed asymmetric processes, offering some of the most synthetically useful and widely applicable methods to have emerged from the field [1, 2]. In this chapter we review a subsection of this area, namely, covalently activated organocatalytic asymmetric oxidation reactions. Here, covalent activation will be considered as the catalytic activation of the stoichiometric oxidant through the formation of new covalent bonds between the oxidant and the catalyst. Key developments prior to a similar review [2] are summarized, along with a more detailed account of advances since 2006. Prolinol- and imidazolidinone-catalyzed oxidation reactions, where the substrate rather than the oxidant may be covalently activated, are covered elsewhere in this publication (Chapters 2 and 3).

19.1
Alkene Epoxidation [3, 4]

The development of the Sharpless Ti/tartrate-catalyzed asymmetric epoxidation of allylic alcohols marked the first major breakthrough in the field of asymmetric alkene epoxidation [5]. Although limited to a specific substrate class, the high enantioselectivities and the predictability of the stereochemical outcome have resulted in a valuable and much utilized synthetic transformation. A further significant advance, the Jacobsen–Katsuki epoxidation, utilizes Mn-salen catalysts for the asymmetric epoxidation of unsubstituted alkenes (alkenes lacking a coordinating group), and offers an additional highly useful method of asymmetric alkene epoxidation, although often giving low selectivities for trans and terminal alkenes [6].

Since then several organocatalytic methods of asymmetric alkene epoxidation have been developed, offering highly useful metal-free catalytic systems. The most successful of these are based on the activation of the triple salt Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), of which $KHSO_5$ is the active component. Three major classes of organocatalysts for Oxone-mediated epoxidation have been developed: ketones, iminium salts, and secondary amines or ammonium salts [7]. The latter

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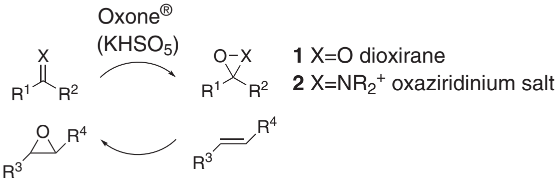
do not proceed via covalent activation and as such will not be covered in this chapter. The two former classes of catalyst stem from studies into the Oxone-mediated activation of ketones to dioxiranes [8]. Both methods of catalysis have been shown to proceed via similar mechanistic pathways with Oxone activation of the ketone or iminium salt precursor to a three-membered reactive heterocyclic intermediate, either the dioxirane **1** or the oxaziridinium salt **2** (Scheme 19.1). It is this heterocyclic intermediate that transfers oxygen to the alkene via a concerted (though possibly asynchronous) pathway. Through the use of a chiral catalytic precursor this proceeds enantioselectivity and stereospecifically, with retention of the original alkene geometry and regeneration of the catalytic ketone or iminium.



Scheme 19.1 Ketone- and iminium salt-catalyzed alkene epoxidation.

19.1.1
Ketone-Mediated Epoxidation

The pioneering work by Curci offered one of the first examples of the use of chiral catalysts in the asymmetric epoxidation of alkenes with Oxone. In this early example the use of chiral ketone (+)-isopinocamphone (**3**, Figure 19.1) afforded low enantioselectivities (<15% ee) and reaction rates in a biphasic solvent system [9]. Subsequently, Yang developed a class of C$_2$-symmetrical ketones **4** that in a monophasic (CH$_3$CN/H$_2$O) solvent system gave improved enantioselectivity [47% ee for the epoxidation of (*E*)-stilbene] [10, 11].

However, it was the development of the fructose-derived ketone catalyst **5**, reported by Shi in 1996, that offered the most useful organocatalyst for asymmetric epoxidations [12–14]. Now commercially available, the catalyst **5** can be produced

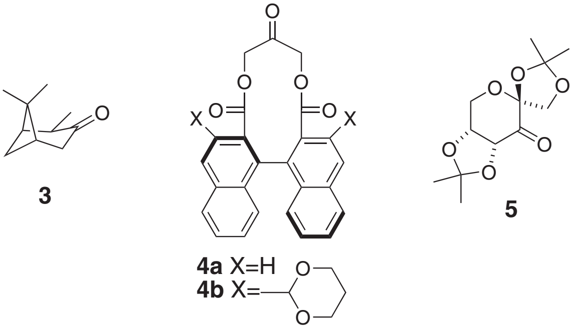
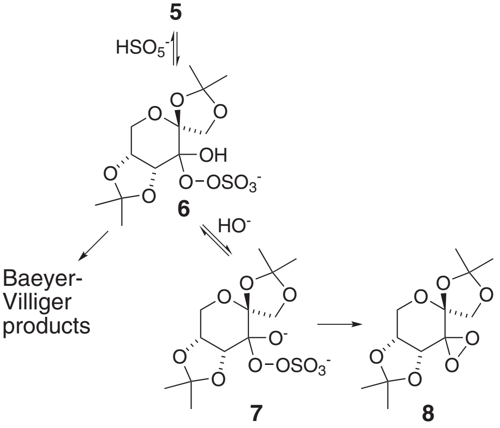
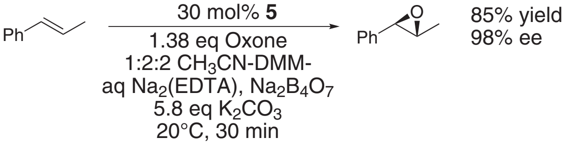


Figure 19.1 Chiral ketone catalysts.

in two steps from D-fructose [15] and the opposite enantiomer obtained in five steps from L-sorbose. While initial studies reported high epoxidation enantioselectivities, they also required high loadings of ketone catalyst (ca. 3 equiv.) due to the decomposition of the catalyst via the Baeyer–Villiger reaction [12]. A raised reaction pH has been found to be the solution to this problem, with an optimum pH proving to be ca. 10.5 [16]. The higher reaction pH favors the formation of anion **7** leading to dioxirane formation, thus reducing the loss of catalyst to decomposition (Scheme 19.2). The new reaction conditions allowed for the use of substoichiometric amounts of the ketone catalyst (typically 20–30 mol%), with a 1 : 2 mixture of CH_3CN and dimethoxymethane (DMM) found to be the preferred solvent system (Scheme 19.3) [13].



Scheme 19.2 Effect of pH on the Baeyer–Villiger reaction of ketone **5**.



Scheme 19.3 Shi epoxidation with ketone **5**.

This catalytic system provides high enantioselectivities for a range of epoxides (Figure 19.2), including those derived from trisubstituted and *trans*-1,2-disubstituted alkenes, with complete stereospecificity (retention of the alkene geometry in the epoxide product) [17]. The reaction has been shown to be chemoselective for the alkene of enynes [18], provided monoepoxides upon reaction with conjugated *trans*-dienes [19] and afforded up to 93% ee for the asymmetric epoxidation of fluoro-olefins [20]. However, decreased enantioselectivity was observed for both *cis*- and terminal alkenes. The catalytic system has also been applied to the resolution and desymmetrization of cyclic trisubstituted alkenes [21].

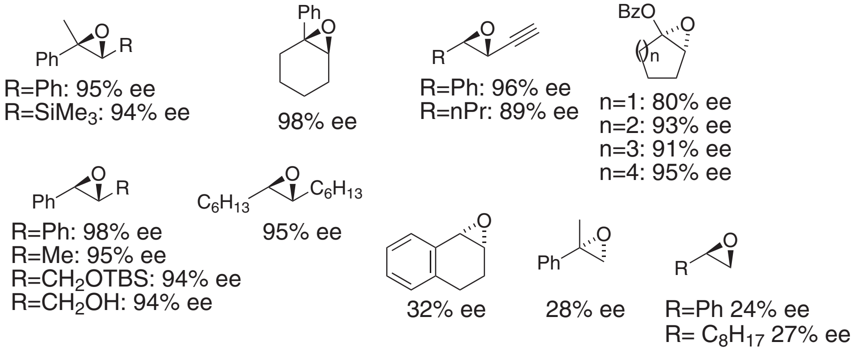
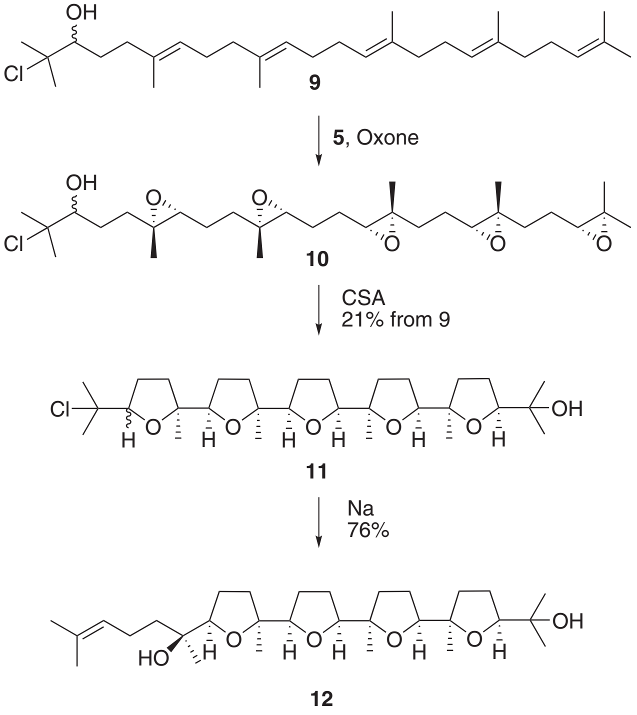


Figure 19.2 Scope of Shi epoxidation with ketone **5**.

The Shi epoxidation has been used in several total syntheses [14]. Of particular note is its use in establishing the stereochemistry of polyepoxides, which can undergo cascade cyclization to polyether products [22, 23], mimicking possible biosynthetic pathways. Corey has put this strategy to use in several natural product syntheses such as the total synthesis of glabrescol [24, 25]; and more recently in the total synthesis of (+)-omaezakinol **12** (Scheme 19.4) [26].



Scheme 19.4 Use of Shi epoxidation in the total synthesis of (+)-omaezakinol (**12**).

One issue with the use of Oxone is the high level of salt waste. As such the use of alternative co-oxidants is desirable. Hydrogen peroxide is attractive due to its high oxygen content and the production of water as a by-product. The use of hydrogen peroxide as an alternative oxidant in ketone **5**-catalyzed epoxidation requires the presence of nitriles, such as CH_3CN [27–29]; it is proposed that a perimidic acid is formed *in situ* by addition of the hydrogen peroxide to the nitrile and that it is this perimidic acid that converts the ketone catalyst into the active dioxirane. Again the reaction pH is crucial to both conversion and enantioselectivity, with a pH of ca. 11 proving to be optimum. Despite the benefit offered by the use of hydrogen peroxide it has been noted that compared to the use of Oxone this procedure is more sensitive to the reactivity and solubility of olefins. As such, optimization of conditions such as catalyst loading, time, temperature, the amount of H_2O_2, and solvent may be required [29].

A reliable model for rationalizing the stereochemistry of the epoxide products has been developed. For the reaction of alkenes with dioxiranes two extreme transition states have been proposed, the spiro and planar modes (Figure 19.3). Because these two extreme modes of approach often lead to the prediction of opposite enantiofacial selectivity based on consideration of steric interactions with substrate substituents, knowledge of any spiro/planar preference is important. Observed experimental evidence along with computational studies indicate the preference for the spiro mode (ca. 7.4 kcal according to B3LYP/6-31G* calculations) [30–32]. This observed preference exists due to the stabilizing secondary orbital interaction between the alkene π*-orbital and a lone pair on the dioxirane oxygen being transferred to the alkene, only available in the spiro mode. When Shi catalyst ketone **5** is used the major enantiomer results from the TS model shown in Figure 19.4, with attack on the less-hindered equatorial dioxirane oxygen in the spiro mode, and an alkene hydrogen substituent placed in the region of the dioxirane's axial α-oxygen substituent. Kinetic isotope studies have provided further support for this model and have identified that the transition state may be significantly asynchronous for certain alkenes [33]. More recently, transition state modeling at the UB3LYP-DFT/6-31G* level of theory has allowed the accurate prediction of enantioselectivity for dioxirane-catalyzed epoxidations, while providing further support for the preference of the spiro TS model [34].

This model also offers an explanation for the poor selectivities achieved in the epoxidations of *cis*- and terminal alkenes, where R = H. With these substrates either enantiotopic face of the alkene can approach the dioxirane oxygen with a hydrogen placed in the spirocyclic acetonide region (R^1 and R^2 interchanged in

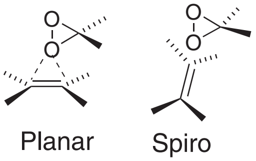


Figure 19.3 Spiro and planar transition states.

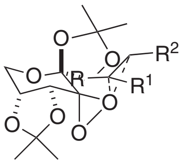
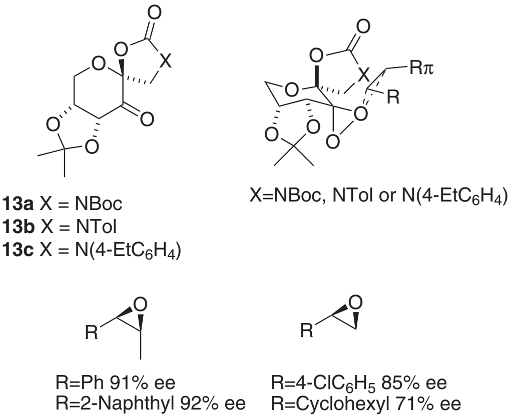


Figure 19.4 Model for enantioselectivity with dioxirane from ketone **5**.



13a X = NBoc
13b X = NTol
13c X = N(4-EtC_6H_4)

X=NBoc, NTol or N(4-EtC_6H_4)

R=Ph 91% ee
R=2-Naphthyl 92% ee

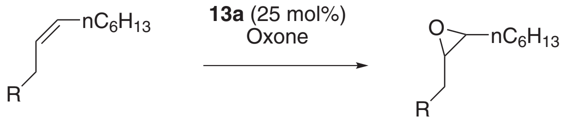
R=4-ClC_6H_5 85% ee
R=Cyclohexyl 71% ee

Figure 19.5 Epoxidation of *cis*- and terminal alkenes with ketone **13;** epoxidation examples with catalyst **13a**.

Figure 19.4). Shi reasoned that modification of the spirocyclic substituent to one capable of differentiating between the R^1 and R^2 substituents would overcome this issue. This led to the development of the novel oxazolidinone catalysts **13**, produced in six steps from D-glucose [35]. With this catalyst class, good enantioselectivity has been achieved with conjugated *cis*-alkenes and styrenes [36–38]. The major enantiomer can be predicted from the transition state model shown in Figure 19.5, where the oxazolidinone substituent is suggested to have an attractive interaction with the π-substituent on the alkene [39–42]. Good enantioselectivity for *cis*-disubstituted alkenes make this chemistry complementary to the Jacobsen–Katsuki Mn(salen) catalyzed epoxidations.

The development of the oxazolidinone catalyst has allowed Shi to further increase the scope of the epoxidation to a range of new substrates. Using ketone catalyst **5** styrene is epoxidized with 24% ee, while the use of oxazolidinone **13a** for the same transformation gave 86% ee, with further improvement in enantioselectivity seen with the inclusion of electron-donating substituents on the aromatic ring of the styrene substrates [43]. *cis*/*trans*-Dienes and trienes were epoxidized regioselectivity at the *cis*-alkene and no isomerization or further epoxidation of the products were observed [44], while epoxidation of conjugated *cis*-enynes resulted in chemoselective epoxidation of the alkene [45].

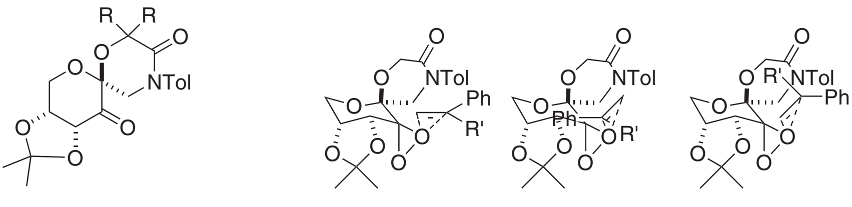
A study on the epoxidation of non-conjugated *cis*-olefins with oxazolidinone catalyst **13** has shown that hydrophobic and electronic interactions between the substituent and the catalyst can have a significant role in the selectivity of the reaction (Scheme 19.5) [46]. *cis*-Alkenes containing two substituents with very different hydrophobic/electronic properties can provide good systems for asymmetric epoxidation as they further reinforce preference for the favored spiro transition state seen above in Figure 19.5.



R = H, 52% yield, 64% *ee*
R = OH, 71% yield, 79% *ee*

Scheme 19.5 Asymmetric epoxidation of non-conjugated *cis*-alkenes.

Despite the improved yields seen for *cis*- and terminal alkenes with the use of oxazolidinone catalysts **13** the epoxidation of 1,1-disubstituted terminal alkenes remained a challenge. For example, catalyst **13a** only afforded 33% ee for the epoxidation of α-methylstyrene. Despite the poor results, it was inferred from the absolute configuration of the products that the epoxidation of 1,1-disubstituted terminal alkenes proceeds through a preferred planar transition state. This led to the development of a new lactam catalyst **14a**, which was found to afford higher enantioselectivities (up to 88% ee for a range of 1,1-disubstituted alkenes) [47]. With this catalyst Shi suggests that the six-membered lactam moiety provides a more favorable environment, compared to catalysts **5** and **13**, for attraction between the lactam moiety of the ketone and the phenyl group of the aromatic terminal alkenes. As a result the planar transition state shown in Figure 19.6 is favored over competing spiro transition states. A second planar transition state (where R′ and Ph are interchanged), leading to the minor product enantiomer, can be



14a R = H
14b R = Me

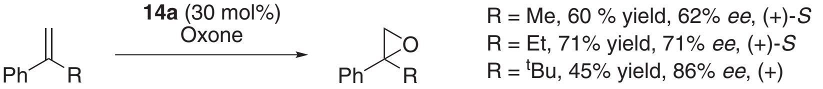
Favored
Planar TS

Spiro TS **1**

Spiro TS **2**

Figure 19.6 Lactam catalyst for the asymmetric epoxidation of 1,1-disubstituted terminal alkenes.

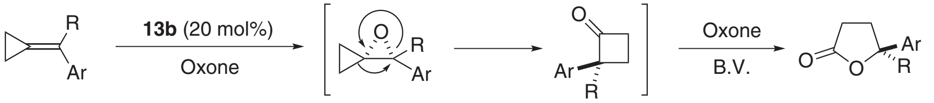
envisaged; however, as with the oxazolidinone catalyst **13**, the origin of the preference for the favored planar transition state is believed to lie in the attractive interaction between the phenyl ring and the lactam moiety of the catalyst. Of the alternative possible spiro-TSs, spiro TS 1 is another possible source of the minor product enantiomer. Spiro TS 2 is likely to be disfavored due to steric interactions between the lactam and the alkene R substituent. The enantioselectivity of the reaction has been found to increase with an increasingly bulky R group on the 1,1-disubstituted terminal alkene, due to the increased steric interactions further disfavoring the spiro transition states (Scheme 19.6).


14a (30 mol%)
Oxone
Ph
R
O
Ph
R
R = Me, 60 % yield, 62% *ee*, (+)-*S*
R = Et, 71% yield, 71% *ee*, (+)-*S*
R = ^{t}Bu, 45% yield, 86% *ee*, (+)

Scheme 19.6 Asymmetric epoxidation of 1,1-disubstituted alkenes using lactam catalyst **14a**.

Previous studies had found that the dimethyl groups on the ketal moiety of ketone catalyst **5** are vital for high enantioselectivities for the epoxidation of *trans* and tri-substituted alkenes [48]. To further study the effect of the sterics of the spiro moiety on the enantioselectivity Shi developed dimethyl-lactam catalyst **14b** [49]. Dimethyl catalyst **14b** was tested with a range of alkenes and found to afford higher enantioselectivity for the epoxidation of *trans* and tri-substituted alkenes compared to lactam catalyst **14a**, suggesting that the dimethyl groups in the α-position of the lactam increase the preference for the spiro transition state. However, the use of dimethyl catalyst **14b** afforded lower enantioselectivities for the epoxidation of conjugated *cis* and terminal alkenes, presumably due to the dimethyl groups weakening the attraction between the phenyl group of the substrate and the lactam moiety of the catalyst.

Shi has also applied oxazolidinone catalyst **13b** to the synthesis of γ-aryl-γ-butyrolactones via an asymmetric epoxidation, ring opening and Baeyer–Villiger oxidation pathway (Scheme 19.7) [50]. The reaction can be stalled after the ring opening to give chiral cyclobutanones through the use of more ketone catalyst and less Oxone. Similarly, asymmetric epoxidation of benzylidene-cyclobutane followed by epoxide rearrangement provides a route to chiral 2-arylcyclopentanones. In this example the epoxide rearrangement can be achieved with either retention or inversion of configuration using LiI or Et_2AlCl, respectively (Scheme 19.8) [51].



Ar = pMePh, R = H: 91% ee
Ar = pMePh, R = Me: 79% ee

Scheme 19.7 Synthesis of chiral γ-aryl-γ-butyrolactones with ketone **13b**.

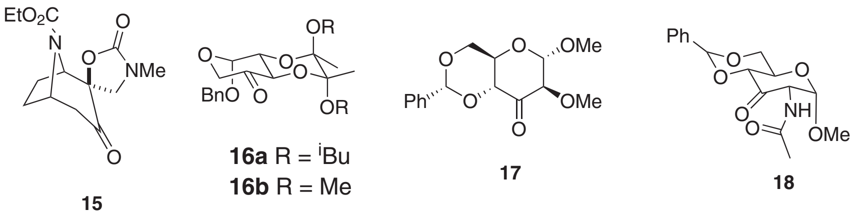
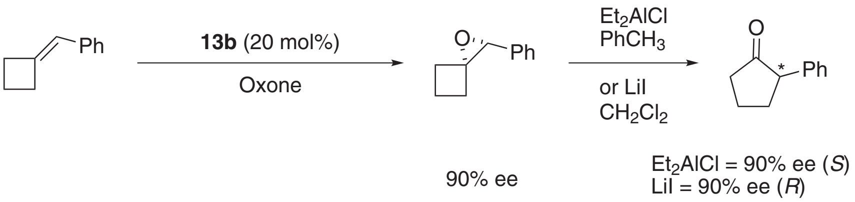


Figure 19.7 Selected chiral ketone catalysts.



Scheme 19.8 Synthesis of chiral 2-arylcyclopentanones with ketone **13b**.

While the Shi catalysts are the most useful both in terms of enantioselectivities and ease of synthesis, several other groups have also made contributions to the design and understanding of ketone catalysts for asymmetric epoxidation [52–61]. Bicyclo[3.2.1]octanones have been shown to be valuable catalysts for asymmetric epoxidation; their general stability to the Baeyer–Villiger reaction has allowed the first example of a supported, recyclable ketone catalyst [62], based on a fluorotropinone motif [63, 64]. In terms of epoxidation enantioselectivity, the best general results to date have been achieved with the inclusion of a spirocyclic substituent in the α-position of the ketone (**15**, Figure 19.7), affording 91.5% ee for the epoxidation of (*E*)-stilbene [65–68].

Several novel carbohydrate-derived ketones have been reported. Arabinose-derived ketone catalyst **16a** has been shown to provide good enantioselectivities for the epoxidation of *trans*-aliphatic alkenes but offered poor enantioselectivity for *cis*-alkenes [69–71]. Studies found that increased enantioselectivities could be achieved for the epoxidation of *cis*-alkenes with decreased size of the acetal blocking groups. The best results for the epoxidation of *cis*-alkenes were found with methoxy catalyst **16b**, which was successfully used in the synthesis of the side chain of Taxol® [72].

Further examples of sugar-derived catalysts can be found in the range of catalysts developed by Vega-Perez and Iglesias-Guerra [73, 74]. Of particular note is the mannose-derived ketone catalyst **17**, affording 90% ee for the epoxidation of triphenylethylene [75]. A novel *N*-acetyl-D-glucosamine catalyst **18** has been developed by Davis, affording up to 81% ee for the epoxidation of styrenes at catalyst loadings of 6 mol% [76].

Owing to their electron-poor nature, enoates present challenging substrates for asymmetric oxidation using the electrophilic dioxirane reagents previously

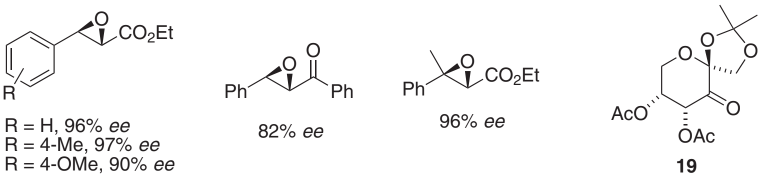


Figure 19.8 Scope of asymmetric oxidation of electron-deficient alkenes with bis-acetate catalyst **19**.

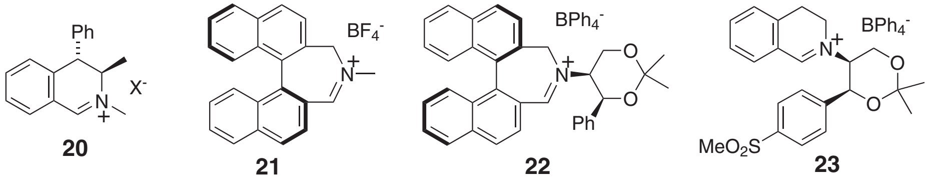


Figure 19.9 Chiral iminium salt catalysts.

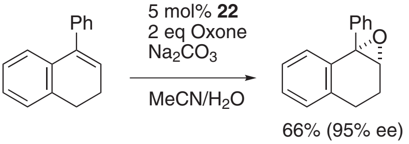
discussed. The often slow reaction times allow for increased decomposition of the catalysts or the Oxone. Despite this some promising examples of dioxirane-mediated enoate epoxidation can be found. Fluoroketones have been shown to epoxidize (*E*)-cinnamate esters with moderate reactivity and selectivity [63, 64] and catalysts related to **16** have afforded up to 81% ee for the epoxidation of (*E*)-cinnamate [71].

Shi has also provided examples of enoate epoxidation using a modified version of his fructose-derived catalyst, bis-acetate **19** with more electron-withdrawing ester groups in place of the acetonide unit in **5** [77, 78]. Use of bis-acetate catalyst **19** has provided excellent enantioselectivities for both the epoxidation of α,β-unsaturated esters and *trans*-cinnamate esters (Figure 19.8), affording 96% ee for the epoxidation of *trans*-ethyl cinnamate [79]. The use of Yang's catalyst **4** also allowed the epoxidation of cinnamates, affording 74% ee for (*E*)-methyl cinnamate and up to 92% ee with increased steric bulk at the 4-position of the substrate's aryl ring [80].

19.1.2
Iminium Salt-Catalyzed Epoxidation

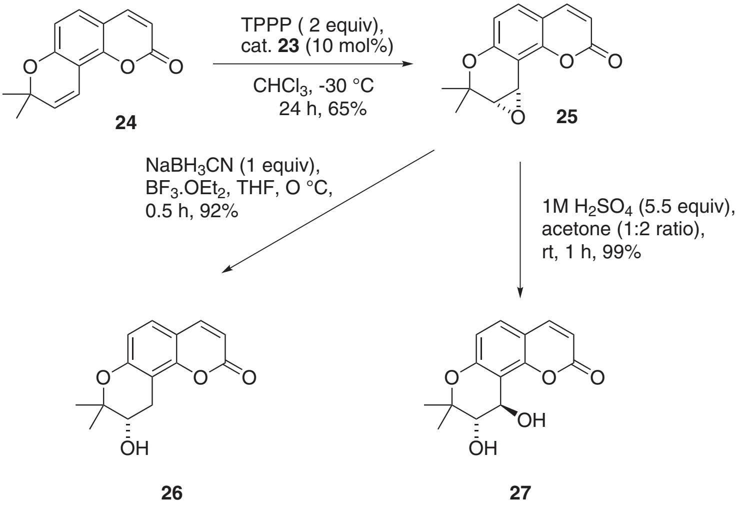
Proceeding via a similar reaction mechanism to the ketone-mediated epoxidation reactions, iminium salts offer an alternative source of catalysts for asymmetric organocatalytic epoxidations. The first example of the application of iminium salts to asymmetric epoxidations used dihydroisoquinolinium-based catalyst **20** (Figure 19.9), affording a 33% ee for the epoxidation of (*E*)-stilbene [81].

Aggarwal subsequently reported the use of a chiral binaphthyl iminium-salt **21**, giving 31% ee for the epoxidation of (*E*)-stilbene and 71% ee for the epoxidation of 1-phenylcyclohexene [82]. Several alternative iminium catalysts have been tested [83], as well as the *in situ* production of iminium salts from amines and aldehydes [84]. However, enantioselectivities remained low until in 2004 Page reported the use of modified versions of binaphthyl iminium salt containing exocyclic chirality,

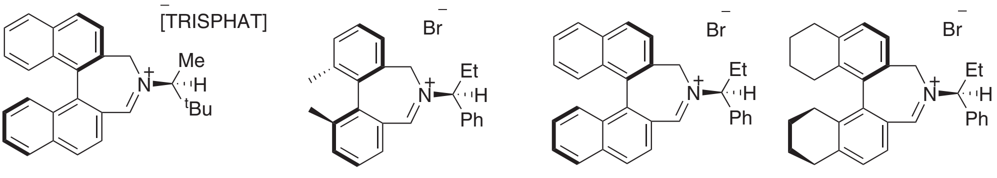


Scheme 19.9 Asymmetric epoxidation with iminium salt **22**.

for example, catalyst **22** (Scheme 19.9). These modified versions of Aggarwal's binaphthyl iminium salts resulted in up to 95% ee being obtained for cyclic aromatic alkenes [85–87]; and notably afforded 91% ee for the epoxidation of 1-phenylcyclohexene at catalyst loadings of 0.5 mol%. One issue was the aqueous reaction conditions required, due to the poor solubility of Oxone in organic solvent, preventing low temperatures from being used [88]. To overcome this, Page developed a non-aqueous reaction system using tetraphenylphosphonium monoperoxysulfate as a co-oxidant, in place of Oxone [89]. While $CHCl_3$ was found to be the solvent of choice for this non-aqueous reaction system, a switch to MeCN in several cases can be used to obtain the opposite enantiomer in similar yields; for example, the epoxidation of 1-phenylcyclohexene in MeCN afforded the (–)-(1*S*,2*S*) epoxide with 45% ee, while in $CHCl_3$ the (+)-(1*R*,2*R*) product is obtained in 48% ee [90]. As with the dioxirane-mediated epoxidations alternative stoichiometric oxidants have also been tested with the iminium-catalyzed epoxidation reaction; examples include sodium hypochlorite with carbonates [91] and hydrogen peroxide [92]. Conditions for the electrochemical generation of both percarbonate and persulfate oxidants have also been developed [93]. This reaction system combined with catalyst **23** allowed the highly enantioselective epoxidation of alkene **24**, a key step in the enantioselective synthesis of both (–)-(3′*S*)-lomatin (**26**) and (+)-(3′*S*,4′*R*)-*trans*-khellactone (**27**) (Scheme 19.10) [94].



Scheme 19.10 Asymmetric synthesis of (–)-(3′*S*)-lomatin (**26**) and (+)-(3′*S*,4′*R*)-*trans*-khellactone (**27**).

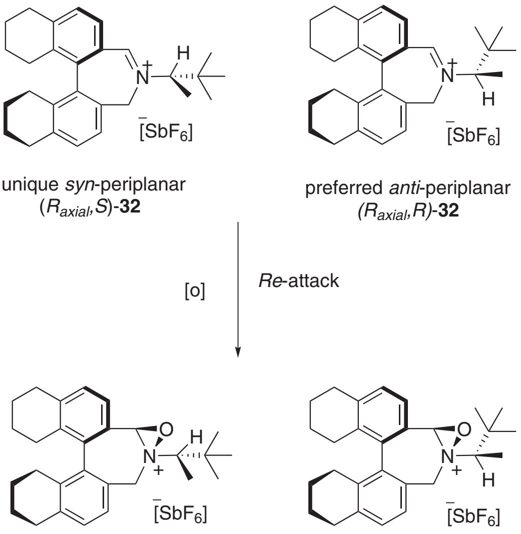


28 **29** **30** **31**

Figure 19.10 Azepinium catalysts [(R_{axial},S)-configuration depicted in all cases].

Lacour has developed a similar biaryl azepinium salt catalyst **28** with an exocyclic chiral carbon center; these catalysts have provided up to 86% ee for the epoxidation of 1-phenylcyclohexene and up to 98% ee for the epoxidation of trisubstituted allylic alcohols [95, 96]. It has previously been shown that the enantioselectivity of the epoxidation reaction is dominated by the biaryl moiety and not the exocyclic appendage of the binaphthyl azepine catalyst [85, 87, 97]. Lacour has studied this effect further by looking at the series of catalysts **29**–**31** (Figure 19.10) [98]. Comparison of pairs of catalyst diastereomers with the same axial chirality but differing in configuration at the exocyclic stereocenter confirmed that the biaryl chirality determined the configuration of the major epoxide product. However, there was generally an increased level of enantioselectivity with the (R_{axial},R)-diastereomers compared to the (R_{axial},S)-diastereomers. Lacour studied the effect of the biaryl angle on the enantioselectivity and the relative dominance of the biaryl chirality over the exocyclic chirality. Crystal structures were obtained of either the amine or ammonium salts to calculate the biaryl dihedral angle and it was found that the dihedral angles are in the relative order **29** < **30** < **31**. Assuming the same trend in biaryl angles can be applied to the iminium salts, it was found that the enantioselectivity of the epoxidation reaction increased with the biaryl angle. The difference in ee-values obtained for the diastereomers was found to be lower with an increased dihedral angle, thus suggesting an increased dominance of the biaryl chirality over the exocyclic chirality at increased biaryl angles.

NMR studies of the conformation of two diastereoisomers of azepine catalyst **32** have provided an explanation for the observation that both exocyclic-diastereomers give the same absolute configuration of epoxide product, as well as for the lower reactivity of (R_{axial},R)-**32** compared to (R_{axial},S)-**32** [99]. The explanation lies in the existence of N(sp^2)–C(sp^3) rotamers. The (R_{axial},S)-diastereomer has been shown to exist as a single unique *syn*-periplanar rotamer while the (R_{axial},R)-diastereomer exists as a mixed population of the preferred *anti*-periplanar (shown in Scheme 19.11) and *syn*-periplanar rotamers. Both the unique rotamer for (R_{axial},S)-diastereomer and the preferred rotamer of (R_{axial},R)-diastereomer reinforce a *Re*-attack of the oxidant on the iminium species, giving rise to the same configuration of the oxaziridinium products (Scheme 19.11). Furthermore, it is the mixed population of rotamers of the (R_{axial},R)-diastereomer that is thought to slow the formation of the oxaziridinium intermediate, thus accounting for the lower reactivity observed.



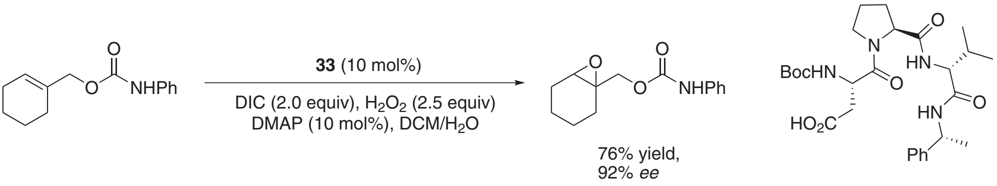
Scheme 19.11 Explanation of observed absolute configuration with the use of azepinium catalyst **32**.

The same study also highlighted problems with the use of tetraphenylborate as a counterion for iminium catalysts. It was noted that under oxidative conditions decomposition of the tetraphenylborate occurred, with biphenyl being produced as a by-product. This affects both the solubility and partition ability of the iminium and oxaziridinium species and as such can have significant effects on the enantioselectivity of the reaction.

Studies [100–102] into the transition state of the iminium salt-catalyzed epoxidations of alkenes suggest that they proceed via spiro-transition states, as with their dioxirane equivalents. However, iminium epoxidations are generally more substrate-specific than their dioxirane counterparts and, as such, producing models to explain the observed trends in stereocontrol has been more difficult. Two major complications are the possibility of producing diastereomeric oxaziridinium salts from most of the iminium catalysts and the large effect reaction conditions can have on enantioselectivity, for example, the solvent effect discussed above. Despite this, some progress has been made. The enantioselectivity of epoxidations using Aggarwal's catalyst **21** has been studied via computational methods by Houk [100] and a study by Breslow highlights the importance of hydrophobic interactions in asymmetric iminium salt catalyzed epoxidations [103, 104]. Studies comparing the reactivity of iminium salts to that of their amine counterparts (reacting via *in situ* oxidation to the iminium salts) have found that iminium salts tend to afford higher enantioselectivities, although marginally so in many cases [97].

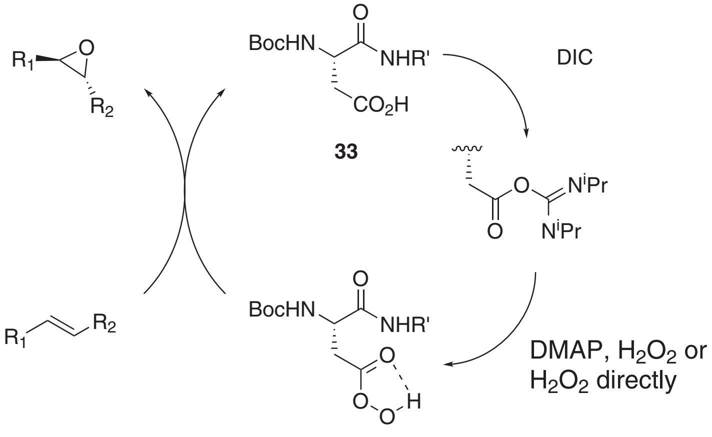
19.1.3
Aspartate-Derived Peracid Catalysis

Peracids represent classic reagents for alkene epoxidation. However, early attempts at asymmetric epoxidation using chiral peracids generally afforded low enantioselectivities [105]; moreover, developing a catalytic system proved challenging. In 2007 Miller made a significant advance towards solving both problems in developing a novel aspartate peptide-derived catalyst **33** for the epoxidation of allylic carbamates [106]. Enantioselectivities of up to 92% ee have been achieved using a catalytic system with hydrogen peroxide, *N,N′*-diisopropylcarbodiimide (DIC) and 10 mol% DMAP (Scheme 19.12). In this catalytic system the carbodiimide-mediated activation of catalyst **33** to peracid **34** is followed by oxygen transfer to the alkene substrate (Scheme 19.13). The DMAP is required to prevent the build-up of an off-cycle, catalytically inactive diacyl-peroxide intermediate. Subsequent studies have highlighted the importance of the two primary amide groups to the activity of the catalyst and have shown that the Boc-protected amine is not involved in substrate–catalyst hydrogen bonding [107]. Currently, scope is limited to homoallylic carbamates, as it is thought that the carbamate functionality facilitates catalyst–substrate interaction through hydrogen bonding.


O
NHPh
33 (10 mol%)
DIC (2.0 equiv), H_2O_2 (2.5 equiv)
DMAP (10 mol%), DCM/H_2O
O
NHPh
76% yield,
92% *ee*
BocHN
HO_2C
N
O
HN
HN
O
Ph

33

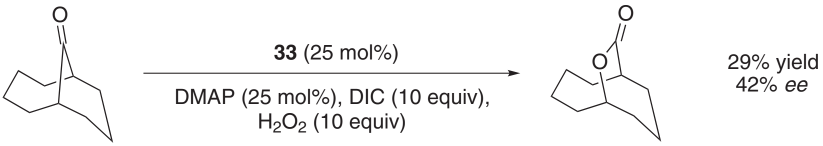
Scheme 19.12 Asymmetric epoxidation of homoallylic carbamates with aspartate derivative **33**.



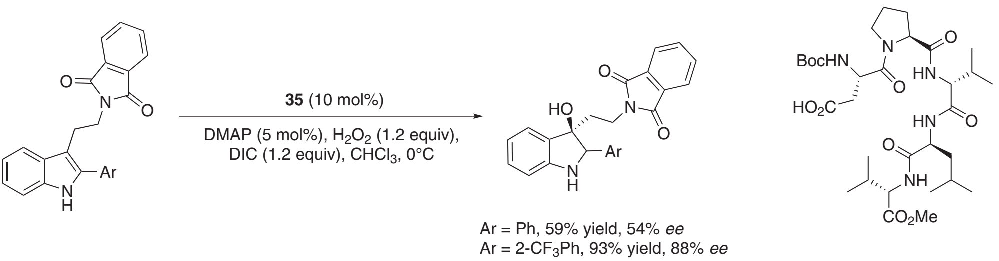
34

Scheme 19.13 Proposed catalytic cycle for asymmetric epoxidation using catalyst **34**.

Miller has found further uses for this catalyst in the asymmetric Baeyer–Villiger reaction (Scheme 19.14), obtaining moderate yields and enantioselectivities [108], and a further modified aspartate catalyst **35** has been applied to chemoselective and enantioselective oxidation of indole (Scheme 19.15) [109].



Scheme 19.14 Asymmetric Baeyer–Villiger oxidation with aspartate-derived catalyst **33**.


35 (10 mol%)
DMAP (5 mol%), H_2O_2 (1.2 equiv),
DIC (1.2 equiv), $CHCl_3$, 0°C
Ar
HO
Ar = Ph, 59% yield, 54% *ee*
Ar = 2-CF_3Ph, 93% yield, 88% *ee*
Ar = 4-MeOPh, 64% yield, 50% *ee*
BocHN
HO_2C
CO_2Me

35

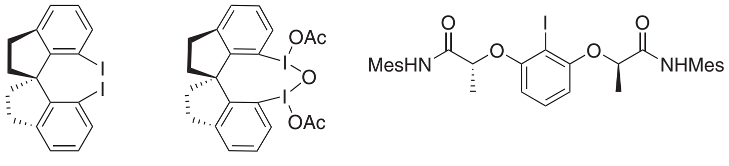
Scheme 19.15 Asymmetric oxidation of indole with peptide catalyst **35**.

19.2
Hypervalent Iodine-Catalyzed Oxidations

Hypervalent iodine reagents, often produced *in situ* from iodoarenes, offer mild and effective oxidants for a range of reactions [110–112]. The past decade has seen increased interest in the use of hypervalent iodine compounds as oxidants due to their mild reactivity, stability, and cost, all of which make them amenable for use on a large scale. With this increased interest, asymmetric reactions are in particular demand [113, 114].

19.2.1
Asymmetrical Naphthol Dearomatization

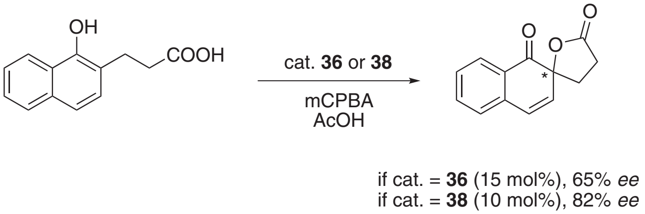
In 2008 Kita developed a procedure for the asymmetric dearomatization of naphthols via the formation of *ortho*-spirolactones using a C_2-symmetrical chiral precatalyst **36** (Figure 19.11) and co-oxidant mCPBA with acetic acid [115] (Scheme 19.16). This reaction proceeds via the mCPBA/acetic acid-mediated oxidation of precatalyst **36** to the hypervalent iodine(III) active catalytic species **37**. Ishihara has taken this work further with the development of the conformationally more flexible chiral organo-iodine precatalyst **38** [116], offering increased enantioselectivity at



36 **37** **38**

Figure 19.11 Chiral organo-iodine catalysts for asymmetric dearomatization of naphthols.

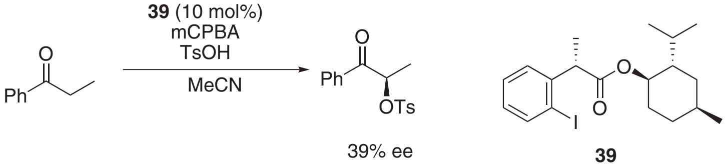
lower catalyst loading, though the scope is currently limited to naphthol derivatives (Scheme 19.16).


OH
COOH
cat. **36** or **38**
mCPBA
AcOH
O
*
if cat. = **36** (15 mol%), 65% *ee*
if cat. = **38** (10 mol%), 82% *ee*

Scheme 19.16 Asymmetric dearomatization of naphthols using hypervalent iodine catalysts.

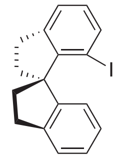
19.2.2 Enantioselective α-Oxysulfonylation of Ketones

In 2008 Wirth developed the first example of the α-oxysulfonylation of ketones using hypervalent iodine catalysts with mCPBA and TsOH (Scheme 19.17) [117]. The best results were achieved with precatalysts containing esters with two chiral centers; however, long reaction times of up to 2–4 days were needed. The reaction is proposed to proceed through a chiral Koser-type chiral hypervalent iodine active catalyst (ArIOTs) formed from the reaction of the precatalyst **39** with mCPBA and TsOH.



Scheme 19.17 Enantioselective tosylation of propiophenone using iodine precatalyst **39**.

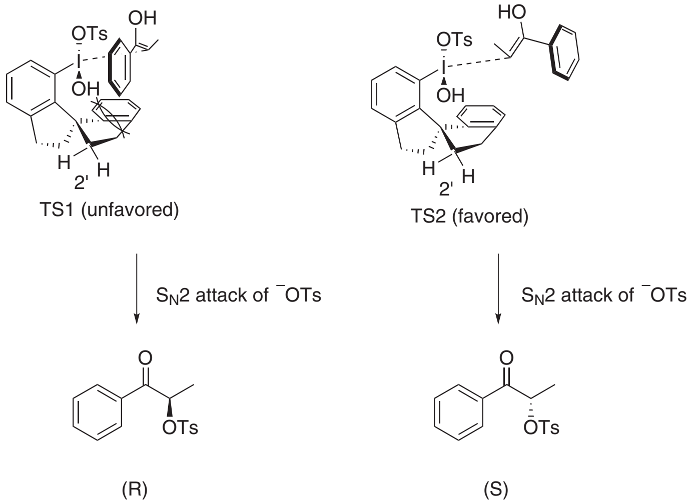
Subsequent work by Zhang optimized the reaction further, obtaining a 53% ee of the (*S*)-enantiomer product (with some racemization of the product under reaction conditions) using precatalyst **40**, Figure 19.12, and changing the solvent to EtOAc [118]. Zhang has also proposed a reaction model to explain the observed



40

Figure 19.12 Chiral iodoarene precatalyst for the asymmetric tosylation of ketones.

configuration of the products. In this model the preferred transition state TS2 (Scheme 19.18) minimizes the steric interaction between the methylene group at the C2′ position of the chiral oxidant and the phenyl ring of the propiophenone. This results in attack of the Koser-type intermediate from the *Re*-face, giving the (*S*)-product configuration after subsequent attack of tosylate with S_N2-inversion

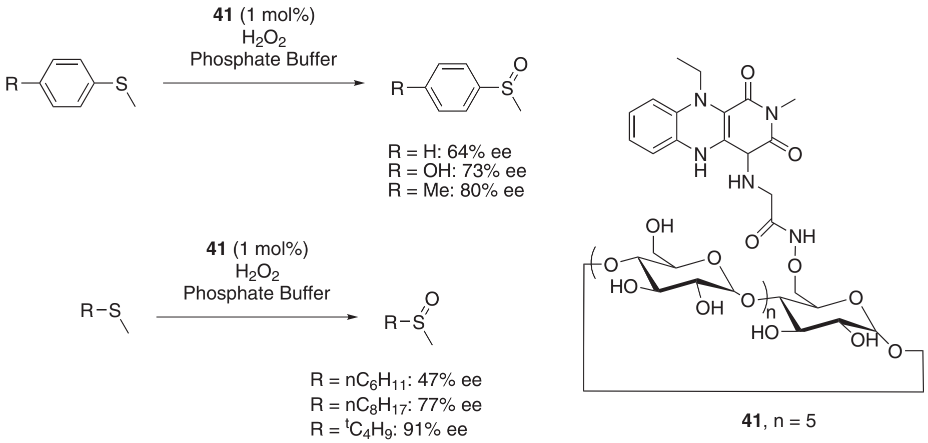


Scheme 19.18 Proposed model for the asymmetric tosylation of ketone using precatalyst **40**.

19.3
Oxidation of Thioethers and Disulfides

The hydrogen peroxide-mediated oxidation of *p*-tolyl methyl sulfide with chiral iminium salt **20** (Figure 19.9), reported in 1993, gives a 32% ee [81]. The use of chiral flavinium salt catalysts afforded a 65% ee for the same transformation [119].

More recently, Kraus has reported the use of flavin-cyclodextrin conjugate catalyst **41** for the asymmetric oxidation of both aromatic and aliphatic methyl thioethers, using hydrogen peroxides in a phosphate buffer (Scheme 19.19) [120, 121].



Scheme 19.19 Oxidation of thioethers with flavin-cyclodextrin catalyst **41**.

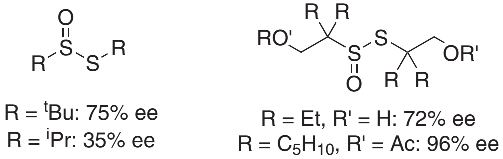


Figure 19.13 Scope for oxidation of disulfides using Shi's ketone catalyst **5**.

The selective oxidation of disulfides to their mono-oxides has been achieved using Oxone and the Shi ketone catalyst **5** (Figure 19.1). The results show promising levels of enantioselectivity, but suffer from limited scope (Figure 19.13). The oxidation of aliphatic disulfides proceeded in up to 75% ee [122], and the oxidation of more sterically hindered hydroxyl disulfides with up to 96% ee [123].

19.4
Resolution of Alcohols by Oxidation

Adam's work into the asymmetric oxidation of alcohols using the Shi ketone catalyst **5** highlights an interesting feature of dioxirane chemistry, namely, their ability to oxidize C–H bonds, including the oxidation of alcohols [124, 125]. He applied this to the desymmetrization of *meso*-stilbene diol or kinetic resolution of the DL-isomer, with opposite enantiomers being obtained from each substrate, affording up to 65% ee. More recently, Zhao has reported the use of a Shi oxazolidinone catalyst derivative **13a**, affording greater selectivity (up to 90% ee), for the same transformation (Scheme 19.20) [126, 127].

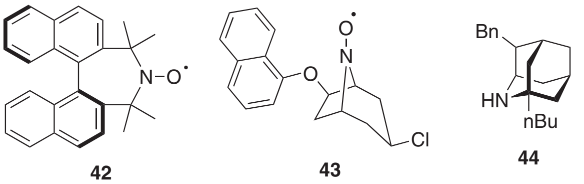
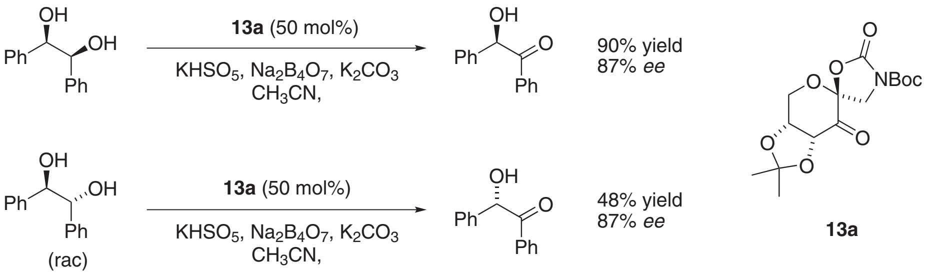
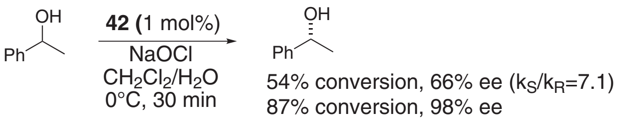


Figure 19.14 Chiral catalysts for oxidative kinetic resolution of alcohols.



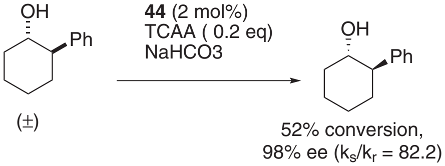
Scheme 19.20 Ketone-catalyzed asymmetric alcohol oxidation.

Rychnovsky has reported an alternative method for the oxidation of secondary alcohols, using chiral nitroxyl radical **42** (Figure 19.14) in the presence of bleach [128]. By analogy to TEMPO oxidations [129], this chemistry is likely to proceed via an oxoammonium ion as the active oxidant. The best substrates were found to be simple benzylic alcohols, giving *S* factors (= k_s/k_r) in the range 3.9–7.1 (Scheme 19.21). Chiral azabicyclo-*N*-oxyl **43** has also been used for the enantioselective electrooxidation of *sec*-alcohols, giving *S* factors of up to 21 [130].



Scheme 19.21 Oxidative kinetic resolution of secondary alcohols using nitroxy radical catalyst **42**.

Chiral 2-azadamantane-*N*-oxyls can also be used for kinetic resolution of secondary alcohols via asymmetric oxidation [131]. *S*-Factors of up to 82.2 were achieved for a range of cyclic and acyclic secondary alcohols using aza-adamantane catalyst **44** (Scheme 19.22).



Scheme 19.22 Kinetic resolution of secondary alcohols using aza-adamantane catalyst **44**.

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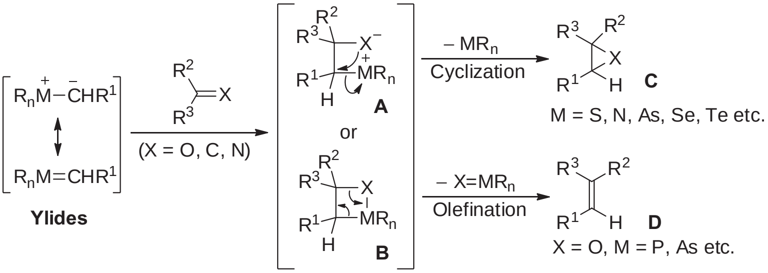
20
Ylides

Saihu Liao, Peng Wang, and Yong Tang

20.1
Introduction

In this chapter we review the applications of ylide-type covalent activation in enantioselective catalytic transformations, in which the association between the catalyst and substrate is established through covalent bond formation in an ylide form. An ylide can be regarded as a nucleophilic carbanion bearing a positively charged heteroatom, which can act as a unique leaving group in a reaction (Scheme 20.1). Traditionally, the addition of the ylidic carbanion to aldehydes, ketones, imines, and electron-deficient olefins gives a betaine (A) or four-membered ring intermediate (B), which can further undergo an intramolecular substitution or β-elimination to expel the heteroatom-containing group, giving the corresponding cyclization (C) or olefination (D) product. The reaction types are mainly dependent on the nature of the heteroatom (M), its substitution (R), and the substrates.



Scheme 20.1 Cyclization and olefination reactions of ylides.

Since the development of the Wittig reaction in the mid-twentieth century [1], the chemistry of ylides grew rapidly. The ylide-based reagents and reactions have become powerful and versatile synthetic tools in organic synthesis, and widely employed in the development of new reactions and the syntheses of natural compounds, biologically active molecules, and pharmaceuticals [2]. However, (super)

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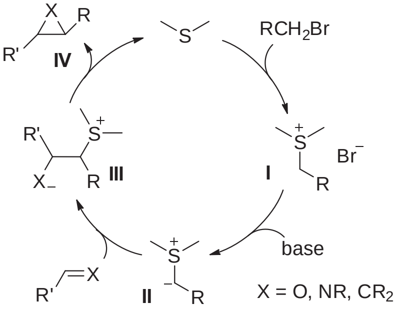
stoichiometric amounts of ylide reagents are normally required in these transformations, and catalytic asymmetric ylide reactions only started to emerge at the end of the 1980s [2a]. Under the renaissance of organic catalysis at the beginning of the twenty-first century and its explosive expansion in the last decade [3], the metal-free inherence of ylide reactions started to draw the attention of organic chemists again and several enantioselective catalytic ylide-based reactions have been developed. In this chapter we describe the development of each element (S, P, N, As, Se, Te etc.) in this area with emphasis placed on recent advances beyond the coverage of Aggarwal's reviews published in 2007 [4].

20.2
Enantioselective Sulfur Ylide Catalysis

Several asymmetric catalytic transformation have been realized via ylidic covalent catalysis, such as epoxidation, aziridination, cyclopropanation, and relevant cyclization reactions, of which sulfide-catalyzed reactions dominate, since sulfides show the best combination of nucleophilicity and leaving-group ability, and also due to the readily availability of non-racemic sulfides [4a–c].

As delineated in Scheme 20.2, a typical catalytic cycle of a sulfide-catalyzed cyclization reaction (epoxidation, aziridination, cyclopropanation) includes mainly four steps: (i) alkylation of the sulfide catalyst to generate the sulfonium salt I; (ii) deprotonation with a base to give the active ylide intermediate II; (iii) addition of the ylidic carbanion to a C=X double bond; and (iv) ring-closure of the betaine intermediate III to give the cyclic product IV and simultaneously regenerate the sulfide catalyst. In the first step, the covalent bond formation between the catalyst and substrate in the ylide catalysis is set through a S_N2-type *substitution*. In the subsequent formation of the active ylide intermediate (II in Scheme 20.1) a *base* is required to abstract the alpha acidic proton. The catalyst is regenerated through an intramolecular substitution. An alternative to this alkylation/deprotonation method of generating ylides is transition metal-mediated carbene-transfer to the sulfide catalysts from a diazo compound under neutral conditions [5].

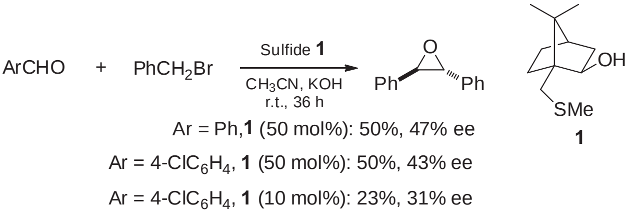


Scheme 20.2 Sulfide-catalyzed ylide reactions: a typical catalytic cycle.

20.2.1
Epoxidation

20.2.1.1 Catalysis via Sulfide Alkylation/Deprotonation

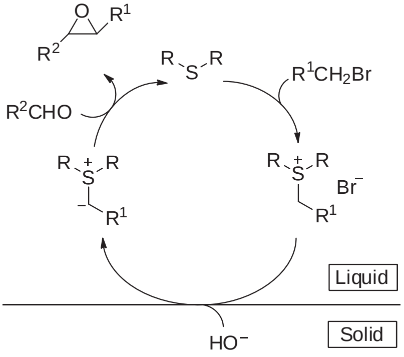
Furukawa and coworkers realized the first enantioselective substoichiometric epoxidation reaction of aldehydes via the sulfide alkylation/deprotonation route, based on their one-pot procedure for the synthesis of oxiranes using sulfides directly rather than the preformed sulfonium salts [6]. In the presence of 50 mol% sulfide **1**, which was prepared in three steps starting from (+)-camphorsulfonic acid, a 50% yield and 47% ee were obtained in the reaction of benzaldehyde with benzyl bromide under solid–liquid two-phase conditions (solid KOH/CH_3CN). A catalyst turnover (TON = 2.3) was also observed when 10 mol% catalyst was used in the reaction of 4-chlorobenzaldehyde (Scheme 20.3). The *O*-methylated derivative of sulfide **1** gave the *trans* epoxides with an opposite configuration.



Ar = Ph, **1** (50 mol%): 50%, 47% ee
Ar = 4-ClC_6H_4, **1** (50 mol%): 50%, 43% ee
Ar = 4-ClC_6H_4, **1** (10 mol%): 23%, 31% ee

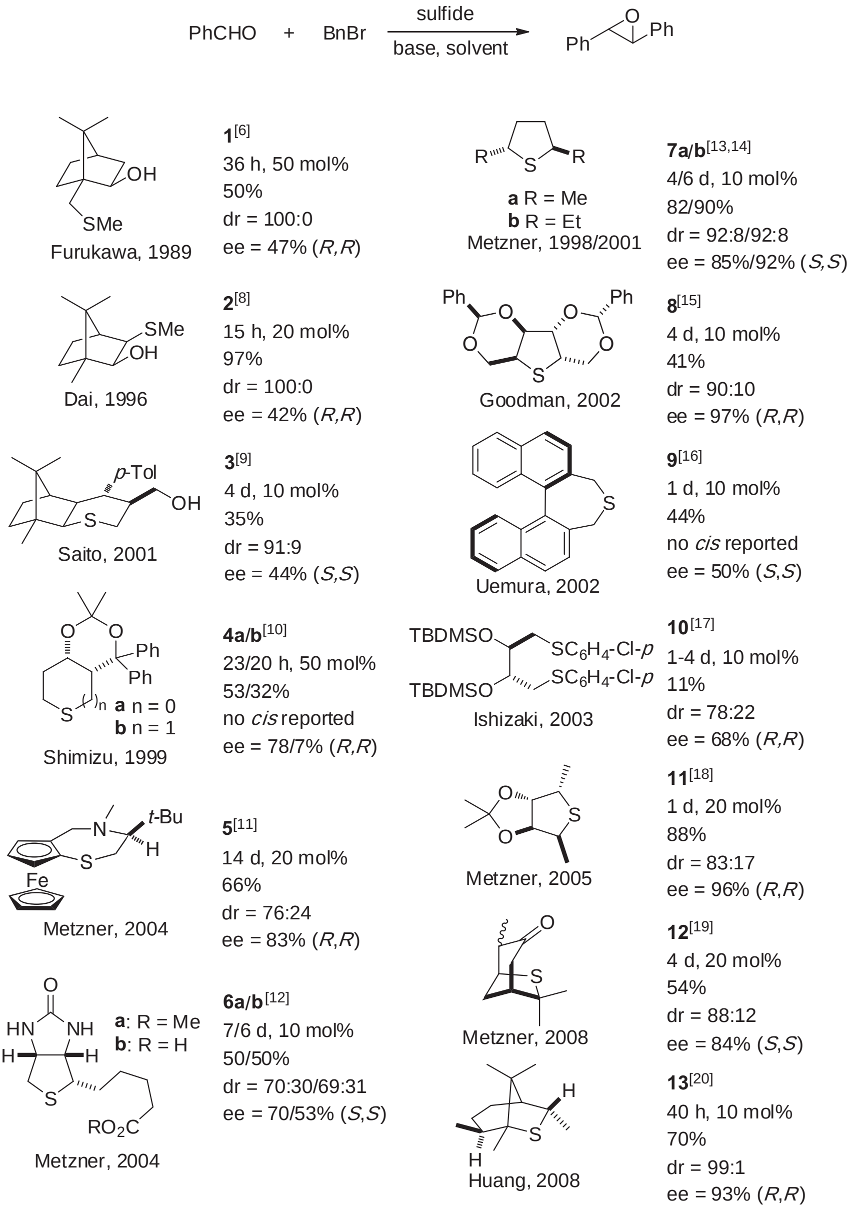
Scheme 20.3 Sulfide-catalyzed enantioselective epoxidation of aldehydes.

The preformed benzyl sulfonium salt produced the oxirane in nearly the same yield and optical purity as the direct use of the sulfide, indicating that the one-pot reaction proceeds via initial formation of the sulfonium salt, which is subsequently deprotonated to generate the ylide *in situ* (Scheme 20.4). The sulfide is finally released upon epoxide ring closure.



Scheme 20.4 Reaction cycle proposed for the formation of oxiranes.

Inspired by this pioneering work, several sulfide catalysts have been developed in the past three decades, aimed at improving the efficiency of this reaction cycle (Scheme 20.5). Some details such as catalyst loading, reaction time, yield, ee value, and configuration obtained in the typical reaction of benzaldehyde with benzyl bromide are also included.



Scheme 20.5 Selected sulfide catalysts for asymmetric epoxidation.

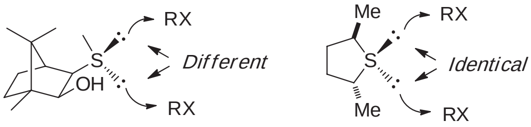
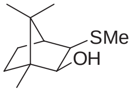
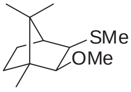


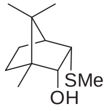
Figure 20.1 Lone pair-selectivity in the alkylation step.



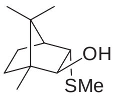
2a



2b



2c



2d

2c-2d

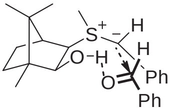


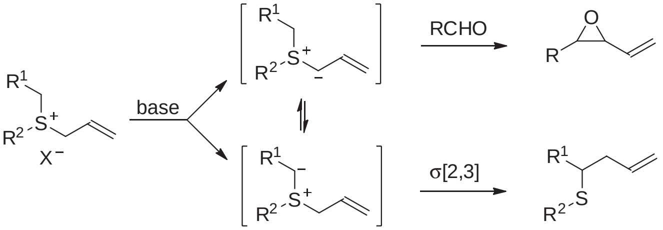
Figure 20.2 Proposed H-bond interaction between the catalyst and aldehydes.

The catalysts in Scheme 20.5 can be roughly divided into two classes: non-C_2-symmetric (**1–6**, **12–13**) and C_2-symmetric (**7–11**) sulfides. In the initial alkylation step generating the sulfonium salts, a C_2-symmetric sulfide can avoid the lone pair selectivity issue, as in this case the two lone pairs at the sulfur atom are identical. In contrast, the alkylation at the two diastereotopic lone pairs of the S atom in non-C2-symmetric sulfides would lead to the formation of two diastereoisomers of the sulfoniums. (Figure 20.1). This lone pair-selectivity can be reflected in the influence of the diastereomeric purity of preformed sulfonium salts on the enantioselectivity [7]. Several chiral sulfides (**1–3** and **13**) lacking C_2 symmetry possess a similar camphor framework.

In 1996, Dai, Huang, and coworkers prepared a series of D-(+)-camphor-derived sulfide **2a–d** (Figure 20.2) [8]. Sulfide **2a** exhibited the highest efficiency in the catalytic epoxidation of benzaldehydes with benzyl bromide, providing exclusively *trans*-stilbene oxide in 97% yield and 42% ee at a 20 mol% catalyst loading. Interestingly, sulfides **2b** and **2c** gave the opposite asymmetric induction. Thus, both enantiomers of the *trans*-1,2-diaryloxiranes are accessible from the same chiral pool-derived [D-(+)-camphor] catalysts.

A H-bond interaction between the free -OH and the carbonyl group of aldehydes (Figure 20.2) was suggested to be crucial in the control of the face-selective approach of the aldehydes to the ylidic carbon, since in the case of *O*-methyl protected sulfide **2b** significantly lower asymmetric induction (4% ee versus 42% ee) was observed. When compared with Furukawa's sulfide **1**, which has a different arrangement of the -SMe and -OH group, the improvement achieved with **2a** in the reaction rate and selectivity may result from the more favored H-bond formation and the more rigid transition structure.

Sulfide **2a** was later employed by Tang and coworkers in the reaction of 4-chlorobenzaldehyde with 3-trimethylsilylallyl bromide for the synthesis of vinyloxiranes. In the presence of 20 mol% of **2a**, the *trans* vinyl epoxide was obtained as the major diastereoisomer in 40% yield and 37% ee [21]. Higher concentrations of both aldehyde and allylic bromide were found to be beneficial to the yields, because the high concentration of allylic bromide favors the formation of the sulfonium salt and the high concentration of aldehyde could probably allow capture of the sulfur ylide before the [2,3]-sigmatropic rearrangement (Scheme 20.6). This reaction with thiolane (THT) as a catalyst could also be carried out without solvent, but the yield was lower than that in *t*-BuOH.

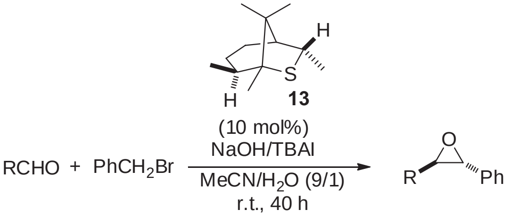


Scheme 20.6 Epoxidation versus [2,3]-sigmatropic rearrangement with allylides.

In 2001, Saito and coworkers reported a cyclic sulfide **3** (Scheme 20.5), which was prepared from camphor via the Diels–Alder reaction of the camphor-derived thiabutadiene with methyl acrylate, followed by reduction of the ester group [9]. In the asymmetric epoxidation of benzaldehyde with benzyl bromide, 44% ee and 35% yield (4 days) was obtained with 10 mol% of the sulfide catalyst. The reaction was slower than that with sulfide **1** and **2a**, which might result from the adjacent hindrance to the sulfur atom or the lack of efficient cooperation of the hydroxyl group as a directing group for aldehydes. Increasing the catalyst loading not only accelerated the reaction but also slightly increased the diastereo- and enantioselectivity. When a stoichiometric amount of sulfide is used, a higher level of enantioselectivity (56–91% ee) can be achieved with a range of aromatic aldehydes.

The most recent sulfide catalyst (**13**) made from D-camphor was reported by Huang and coworkers in 2008, which was obtained via an unexpected Wagner-Meerwein rearrangement of a dimesylate intermediate [20]. Various aromatic aldehydes can be converted into the corresponding *trans* 1,2-diaryl oxiranes in excellent diastereoselectivities (90 to >99% de) and high enantioselectivities (86–96% ee). Notably, this sulfide catalyst is also efficient for aliphatic aldehydes; moderate yields (51–57%) and good enantioselectivities (71–85% ee) were observed with cyclohexane carboxaldehyde, valeraldehyde, and isovaleraldehyde (Table 20.1). Notably, the asymmetric induction was reversed in the case of

Table 20.1 Enantioselective epoxidation of aldehydes with sulfide **13**.

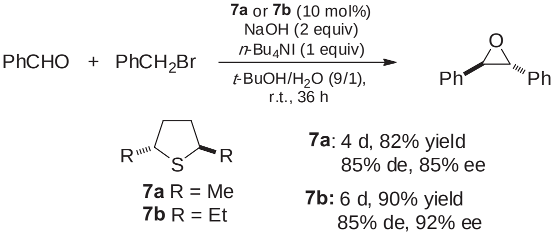


Entry	R	Yield (%)[a]	Trans : cis	ee (%)	Configuration
1	C_6H_5	70	99 : 1	93	(*R*,*R*)
2	4-MeC_6H_4	67	99 : 1	96	(*R*,*R*)
3	4-FC_6H_4	76	100 : 0	88	(*R*,*R*)
4	$2,4\text{-Cl}_2C_6H_3$	80	97 : 3	90	(*R*,*R*)
5	$4\text{-NO}_2C_6H_4$	71	98 : 2	86	(*S*,*S*)
6	2-Furyl	68	95 : 5	86	(*S*,*R*)
7	(*E*)-Styryl	65	99 : 1	85	(*R*,*R*)
8	Cyclohexyl	53	87 : 13	85	(*R*,*R*)
9[b]	$CH_3(CH_2)_3$	57	75 : 25	73	(*R*,*R*)
10[b]	$(CH_3)_2CHCH_2$	51	80 : 20	71	(*R*,*R*)

a) Isolated yield.
b) 15 mol% catalyst, 48 h.

4-nitrobenzaldehyde (entry 5). The levels of stereoselectivity and reaction generality observed make **13** one of the most efficient camphor-derived sulfide catalysts.

A C_2-symmetric sulfide was first employed by Metzner and coworkers in the catalytic epoxidation of aldehydes [13]. The sulfide, (2*R*,5*R*)-dimethylthiolane, which was obtained in two steps from commercially available (2*S*,5*S*)-hexanediol, afforded 94% yield, 85% de, and 90% ee in the stoichiometric reaction of benzaldehyde with benzyl bromide. However, the reaction was very slow at a 10 mol% catalyst loading and required a month to complete. Later, the same group found that the addition of iodide salts like NaI or *n*-Bu_4NI can significantly shorten the reaction time to 2–6 days, with almost conservation of the yields (74–95%) and stereoselectivities (80–85% de and 85–89% ee) [14]. Branched aliphatic aldehydes can also be employed when an equimolar amount of sulfide was used, but the diastereoselectivity fell to a moderate level. Heteroaromatic aldehydes such as 2-furaldehyde and 2-thienylaldehyde could also be epoxidized with good conversion and enantioselectivities (93% and 89% ee, respectively), but special attention has to be paid when isolating these oxirane products, due to their high sensitivity to acids [14]. During the course of reaction optimization, it was found that polar solvents like DMF and DMSO can cause the hydrolysis or solvolysis of benzyl bromide and ether formation [22]. The addition of water to the CH_3CN/KOH solid–liquid biphasic system can efficiently suppress cinnamonitrile formation that was caused by the deprotonation of acetonitrile. Strong bases like Bu^nLi caused ring opening of the thiolane-derived ylides, while $NaHCO_3$ failed to provide the epoxide products. A mixture of Bu^tOH/H_2O (9 : 1) is the optimal solvent for this reaction, which can keep the ylide at a low concentration in order to suppress ring opening of the ylides. A high concentration (e.g., 1 M aldehyde) would decrease the yield of the epoxide due to the Cannizzaro reaction of benzaldehyde. Replacement of (2*R*,5*R*)-2,5-dimethylthiolane with (2*R*,5*R*)-2,5-diethylthiolane can further improve the enantioselectivity from 85% to 92% ee, under the same reaction conditions (Scheme 20.7) [14].



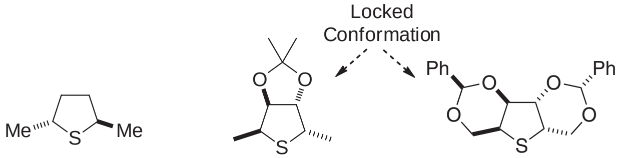
Scheme 20.7 Epoxidation with Metzner's sulfide **7a** and **7b**.

The authors later successfully extended (2*R*,5*R*)-2,5-dimethylthiolane to the allylidene transfer to aldehydes. The epoxidation reaction of benzaldehyde with methallyl iodide gave the desired vinyl oxirane in 60% yield, 50 : 1 dr, and 86% ee. The addition of n-Bu_4NI failed to improve the yields to an acceptable level, probably due to the poor compatibility of this additive with the oxirane products [23].

In 2005, Metzner and coworkers unveiled their second-generation C_2-symmetric sulfide catalysts, which were prepared from D-mannitol, a readily available and cheap chiral source. The new sulfide having an acetal bridge-locked conformation (**11**) provided a remarkable improvement of enantioselectivity in comparison with 2,5-dimethylthiolane (96% ee versus 85% ee, see Figure 20.3) [18]. A change of solvent form Bu^tOH/H_2O to $MeCN/H_2O$ could improve the diastereoselectivity from 83 : 17 to 90 : 10 (trans : cis) with a slightly decreased enantioselectivity (90% ee). n-Bu_4NHSO_4 (20 mol%) was also found to have a positive effect on the reaction rate.

Earlier in 2002, Goodman also reported a D-mannitol-derived sulfide (**8**) containing two acetal moieties to lock the thiolane conformation. This sulfide (10 mol%) provided 97% ee in the reaction of benzaldehyde with benzyl bromide, though only a 41% yield was obtained after 4 days (Figure 20.3) [15].

A type of axial chiral sulfide based on the binaphthyl scaffold was reported by Uemura and coworkers in 2002. In the reaction of benzaldehyde with benzyl bromide in dichloromethane with the addition of n-Bu_4NI, a 44% yield and 50% ee were obtained in 24 h at a 5 mol% catalyst loading. The 3,3′-phenyl derivative **9b** was much less reactive and gave only a trace amount of the epoxide product [16].



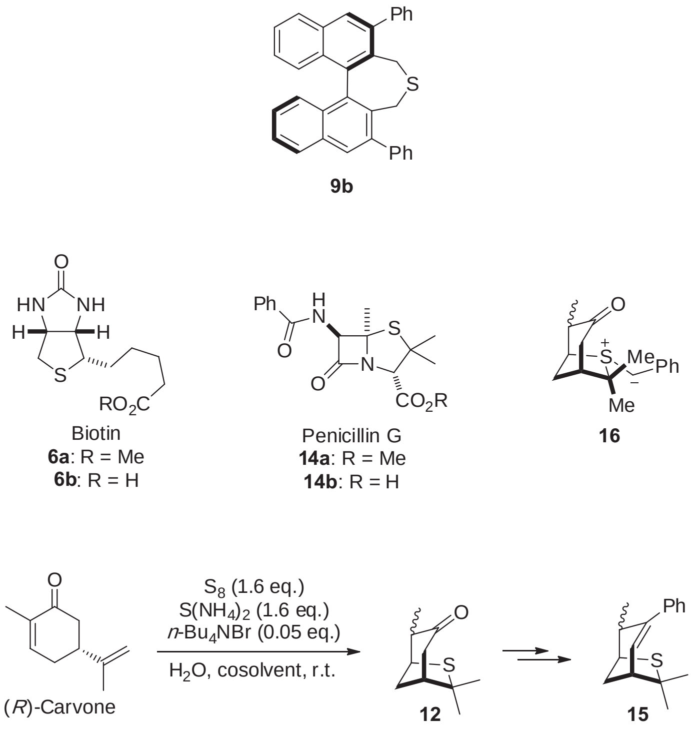
7a (10 mol%)
4 d, 82% yield
85% de, 85% ee

11 (20 mol%)
1 d, 88%
66% de, 96% ee

8 (10 mol%)
4 d, 41%
80% de, 97% ee

Figure 20.3 Development of chiral thiolanes with a locked conformation.

Apart from these synthetic sulfides, some non-racemic naturally occurring compounds, which contain a sulfide moiety and lack a competing functional group for the key epoxidation step, should also be capable of promoting the epoxidation reaction of aldehydes. Reboul, Metzner, and coworker examined the potential of several commercially available compounds, biotin derivatives (**6a,b**) and penicillin G (**14a,b**) (Scheme 20.8), in the reaction of benzaldehyde with benzyl bromide [12]. While penicillin G and its methyl ester failed to promote the reaction, biotin **6b** (10 mol%) gave the epoxide in 50% yield (53% ee) together with a moderate trans/cis selectivity (69 : 31). Better enantioselectivity (70% ee) was observed with its methyl ester-derivative **6a**, but a longer reaction time (6–7 days) was required.

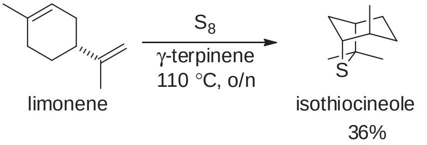


Scheme 20.8 Syntheses of sulfide **12** and **15** from (*R*)-carvone.

Recently, several sulfides with a bicyclo[3.2.1] framework have been developed for the ylide epoxidation reaction. In 2008, Metzner and coworkers prepared several bridged sulfides starting from (*R*)-carvone, which were then evaluated in the epoxidation of benzaldehyde with benzyl bromide (Scheme 20.8). Sulfide **12** was found to be the most enantioselective, delivering the desired *trans* epoxide in 54% yield and 84% ee in 4 days. Sulfide **15**, which was prepared from **12** by reacting with PhLi followed by dehydration, is much more reactive than **12**, providing 80% yield in one day but the enantioselectivity was lower (55% ee) [19].

The *exo*-ylide **16** was presumed to be the major isomer, which was formed by the approach of benzyl bromide from the less hindered convex face of the sulfur atom. Thus the *Re* face of the ylide would be shielded by the downwards methyl group.

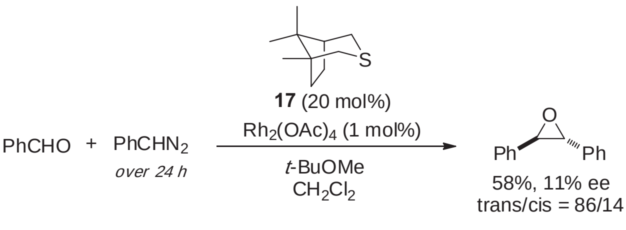
Two years later, in 2010, Aggarwal and coworkers reported the application of isothiocineole, which has a similar structure as **12** and **15** and was prepared via the reaction of limonene with elemental sulfur (Scheme 20.9). In the epoxidation reaction of aldehydes, good yields (56–97%) and high stereoselectivities (60–90% de, 70–98% ee) were obtained with stoichiometric amounts of the preformed benzyl and allyl sulfonium salts [24].



Scheme 20.9 Synthesis of isothiocineole from limonene.

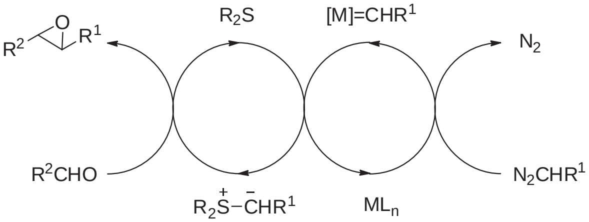
20.2.1.2 Catalysis via Transition Metal-Mediated Carbene Transfer to Sulfides

In catalytic epoxidation reactions an alternative to the ylide generation method via alkylation/deprotonation is the transition metal-mediated carbene transfer from diazo compounds to sulfide catalysts. In 1994, Aggarwal and coworkers employed this method in the enantioselective catalytic epoxidation of aldehydes [25]. Using 20 mol% of non-racemic sulfide **17** and 1 mol% of $Rh_2(OAc)_4$ together with the slow addition of $PhCHN_2$, a 58% yield and 11% ee were obtained in the epoxidation of benzaldehyde (Scheme 20.10). The enantioselectivity was similar to the results obtained by Breau and Durst using preformed sulfonium salts [26].



Scheme 20.10 Catalytic epoxidation via carbene generation of ylides.

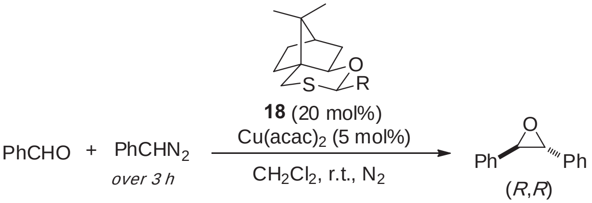
A catalytic cycle was proposed by the authors (Scheme 20.11). Notably, this ylide generation method avoids the use of external bases that are normally required in the alkylation/deprotonation protocols. Therefore, some base-sensitive substrates could also be included into the reaction scope under this “neutral” condition, though the ylide itself is inherently basic. These earlier attempts revealed some important issues that need to be taken into consideration in the future development and improvement of this metallocarbene-containing cycle. Owing to the high reactivity of metallocarbene species, some side-reactions such as the dimerization of diazo compounds and the homologation reaction of aldehydes by reacting with diazo compounds might be involved. The slow addition of diazo compounds, utilization of more nucleophilic sulfides, and increasing the sulfide loadings, which can keep the metallocarbene at a low concentration, could be employed to suppress the dimerization reaction. Since the metallocarbene species are more reactive than alkyl bromide, some less reactive sulfides can also be considered as catalyst candidates. However, in the initial study diphenyl sulfide was found to be inactive; only stilbene, the dimerization product of $PhCHN_2$, was obtained.



Scheme 20.11 Catalytic epoxidation cycle via the metal-mediated carbene transfer route.

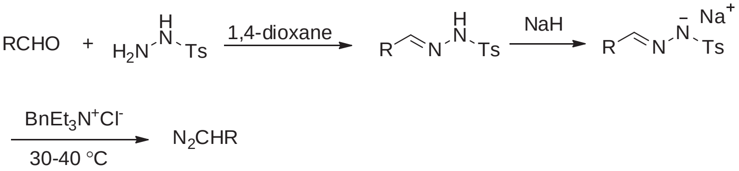
The enantioselectivity was improved significantly to a level of 90% ee by using a type of camphorsulfonyl chloride-derived sulfides (**18**) possessing a thioacetal moiety, which make the R group of the sulfides easily tunable (Table 20.2). However, dry solvent is required, since the thioacetal structure in the catalyst-derived sulfoniums or ylides is unstable in the presence of water [27]. Sterically hindered (entries 3 and 4) or electron-withdrawing R groups (entry 6) resulted in lower yields. The enantioselectivity observed with these thioacetal catalysts was generally at a high level except for **18a**, which lacks a hindered R group to shield one face of the ylide. Sulfide **18b** was the catalyst of choice in terms of yield (73%) and enantioselectivity (93%). A test of the sulfides with a range of aldehydes revealed that aliphatic aldehydes were also compatible with the current reaction conditions, though low yields (around 30%) were obtained. Valeraldehyde was epoxidized with 68% ee and a 92 : 8 trans : cis selectivity, while in the case of cyclohexanecarboxaldehyde a 90% ee was observed but the diastereoselectivity was unsatisfactory (70 : 30, trans : cis). A mechanistic study revealed the high face selectivity to be a result of steric effects (the equatorial methyl group) and electronic effects (a combination of anomeric and Cieplak effects), which both favor aldehyde approach from the *Re*-face of the most stable conformer of the ylides [28].

Table 20.2 Elaboration of sulfide **18** for the epoxidation reaction.



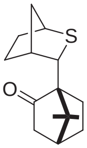
Entry	R	Yield (%)	Trans : cis	ee (%)
1	H (**18a**)	83	>98 : 2	41
2	Me (**18b**)	73	>98 : 2	93
3	Pr^i (**18c**)	45	>98 : 2	93
4	Bu^t (**18d**)	0		
5	CH_2Ph (**18e**)	56	>98 : 2	88
6	CH_2OPh (**18f**)	43	>98 : 2	83
7	CH_2OMe (**18g**)	70	>98 : 2	92

A limitation of the current protocol is the use of diazo compounds, which are potentially explosive and not readily available. The inherent hazards in handling these diazo compounds severely limit the practical application of this methodology. In 2001, Aggarwal and coworkers disclosed a modified Bamford–Stevens reaction [29] for the *in situ* generation of diazo compound from *N*-tosylhydrazone salts. The addition of $BnEt_3N^+Cl^-$ as a phase-transfer catalyst can enable the diazo compound to be produced at 30–40 °C (Scheme 20.12) [30].



Scheme 20.12 *In situ* generation of diazo compounds from hydrazones.

However, attempts to use sulfide **18b** in this process gave the desired epoxides in low yields, which may be resulted from the decomposition of the catalyst under these conditions. The more stable sulfide **19** proved to be the catalyst of choice for this protocol; it can be prepared in four steps from camphor sulfonyl chloride. The combination of 1 mol% $Rh_2(OAc)_4$ and 5 mol% sulfide can promote the epoxidation reaction of a range of aromatic and heteroaromatic aldehydes with high enantioselectivity (up to 94% ee), with the exception of pyridine carboxaldehyde [31].



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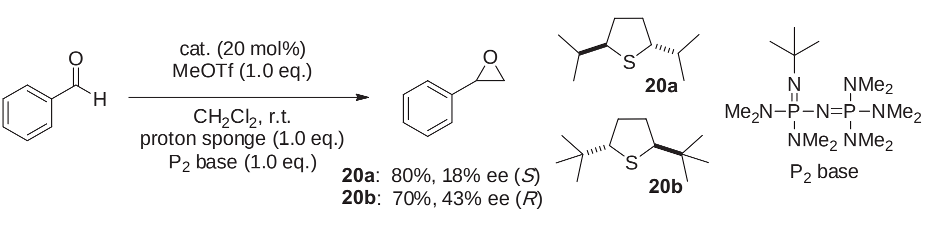
The sulfide-catalyzed enantioselective epoxidation reaction is the most extensively studied transformation in ylide catalysis, and two ylide generation methods (alkylation/deprotonation and carbene transfer) have been developed. Compared with conventional methods for epoxidation via oxygen transfer to the carbon–carbon double bond, such as the Sharpless epoxidation, Jacobsen–Katsuki epoxidation, and Shi epoxidation, the ylide approach can be regarded as an alkylidene transfer reaction to carbonyl groups (C=O), providing a different retrosynthetic analysis for the construction of epoxides. In particular, in the synthesis of vinyl epoxides, the ylide route has priority over conventional oxidation methods, since the issue of regioselectivity in the epoxidation of dienes will not be present [32].

However, several limitations remain in this area such as the lower enantio- and diastereoselectivity in the reactions of simple alkyl aldehydes, and the low yielding epoxidation of ketones. In addition, successful examples in the catalytic ylidic epoxidation of aldehydes are limited to the semi-stable ylides such as arylmethylides (M=CHAr) and allylides (M=CHCH=R_2); the synthesis of simple 1,2-dialkyl oxiranes using the catalytic ylidic route is still elusive. The basic reaction conditions required in the alkylation/deprotonation protocol and the highly reactive metallocarbene species involved in the carbene transfer method often cause some side reactions. Another challenging reaction in this area is the asymmetric methylene transfer used to prepare terminal epoxide from aldehydes. In contrast to benzylidene transfer in the reaction with benzyl bromide, the asymmetric synthesis of terminal epoxides via methylene transfer usually requires (super)stoichiometric loadings of chiral sulfide catalysts, and only moderate enantioselectivity (<60% ee) has been achieved so far [33]. Connon and coworkers recently reported a catalytic asymmetric reaction using MeOTf as the alkylating agent and 20 mol% sulfide **20b** as the catalyst, affording a 70% yield and 43% ee (Scheme 20.13) [34]. MeOTf proved crucial for this success, since methylation of the sulfide proved to be the rate-determining step. In the preparation of the methyl sulfonium salt of

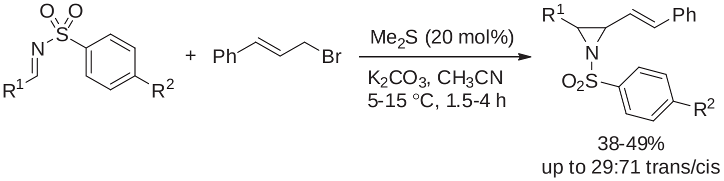


Scheme 20.13 Catalytic ylidic methylene-transfer to benzaldehyde.

thiolane (THT), MeOTf gave a 100% methylation of the sulfide in 24 h, while MeI only gave the desired sulfonium salt in 25% yield, and both MeOTs and MeOMs failed to react with THT.

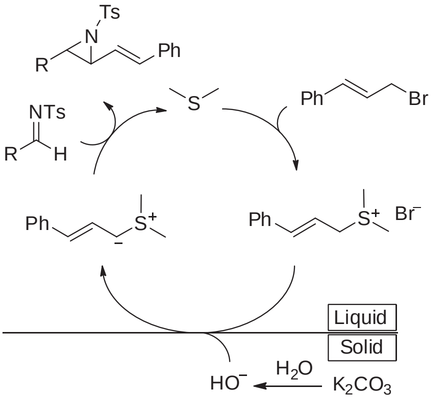
20.2.2
Aziridination

The first sulfide-catalyzed aziridination via an alkylation/deprotonation route was reported by Dai and coworkers in 1996 for the synthesis of vinyl aziridines through the reaction of *N*-sulfonylimines with cinnamyl bromide using dimethyl sulfide (0.2 equiv) as a catalyst (Scheme 20.14). PhSMe and Ph_2S failed to promote this reaction due to the slow alkylation reaction. Chiral sulfide **2** was also tried in this reaction and gave the aziridination product in 23% yield without diastereoselectivity (49 : 51), but no optical yield was reported [35].



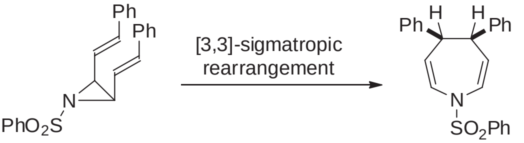
Scheme 20.14 Aziridination of imines for the synthesis of vinyl aziridines.

A similar reaction cycle to the epoxidation of aldehydes was proposed (Scheme 20.15). Obviously, the presence of water would hydrolyze *N*-sulfonylimines to aldehydes and sulfonylamides, which would compete with its reaction with the sulfonium ylides. Other allylic halides like allyl bromide, silylated allyl bromide, and crotonyl bromide were inefficient.



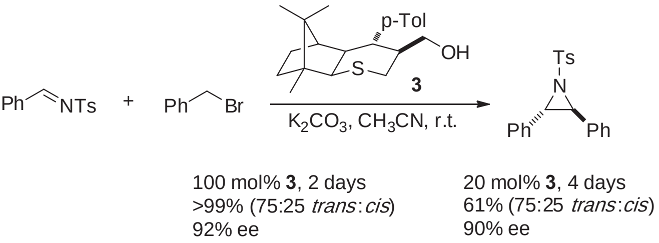
Scheme 20.15 Reaction cycle for aziridination via alkylation/deprotonation route.

A [3,3]-Cope rearrangement product was observed in the reaction of a *N*-sulfonyl α,β-unsaturated imine with cinnamyl bromide (Scheme 20.16).



Scheme 20.16 [3,3]-Cope rearrangement in the reaction of an α,β-unsaturated imine.

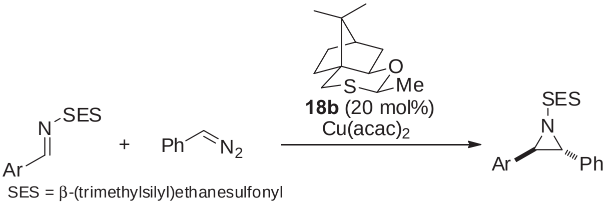
In 2001, Saito and coworkers reported a completely enantioselective catalytic aziridination reaction of *N*-tosylimines with cinnamyl bromide, using sulfide **3**, which has shown good asymmetric induction in the ylidic epoxidation of aldehydes. An electron-withdrawing *N*-sulfonyl group is necessary, since almost no aziridination was observed with aryl, alkyl, and tosylhydrazinyl protected aromatic imines when even an equimolar amount of sulfide **3** was used under similar reaction conditions [36]. Lowering the sulfide loading from 1.0 to 0.2 equivalents in the reaction of *N*-tosyl benzaldimine with benzyl bromide did not erode the enantioselectivity (90–92% ee) and diastereoselectivity (trans : cis = 75 : 25) but decreased the yield from >99% to 61% (Scheme 20.17). Further reduction of the sulfide dosage to 10 mol% resulted in a quite low yield (<10%), but in the reaction with *N*-tosyl cinnamaldimine a 52% yield and 93% ee for the trans isomer can also be obtained in the presence of 10 mol% catalyst.



Scheme 20.17 Enantioselective aziridination of benzaldimine with **3**.

The steps before the ring-closure and simultaneous elimination of sulfide are supposed to be reversible. The steric and electronic effect will influence the reversibility to some extent. The bond rotation step to form a perpendicular arrangement of the sulfonium cation and amide anion in the betaine intermediate is a key step to account for the stereochemical outcome.

Ylide generation via carbene transfer also works well for the aziridination of *N*-sulfonyl-imines [37]. With 20 mol% sulfide **18b** as the catalyst, the reactions of SES-protected imines with diazomethylbenzene provided the aziridine products in moderate yields and high enantioselectivities (85–90% ee), albeit low with trans : cis (ca. 3 : 1) selectivities (Scheme 20.18). The reaction was quite sensitive to the quality of copper sources. When 1.0 equivalent of sulfide was used, slightly better enantioselectivity was observed with $Rh_2(OAc)_4$ but the trans : cis ratios remained the same [38].



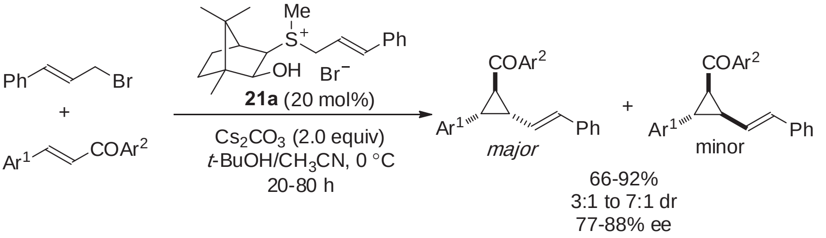
Ar	%Yield	*trans*/*cis*	%ee
Ph	62	3/1	90
4-MeC$_6$H$_4$	50	3/1	88
4-ClC$_6$H$_4$	44	3/1	85

Scheme 20.18 Catalytic aziridination via carbene-transfer route.

The method of *in situ* generation of diazo compounds from *N*-tosylhydrazone salts proved to be quite efficient for aziridination. When sulfide **19** was employed as a catalyst, moderate to good yields and excellent enantioselectivities were obtained with a range of aromatic imines. The trans : cis ratios of the products varied in the range of 2–8 : 1, dependent on the N-protecting group of imines. Notably, the aziridinations of aliphatic imines (cyclohexyl imine, *tert*-butyl imine) and benzophenone-imine also proceeded well, giving the aziridine products in 50–53% yields and 73–98% ee [39].

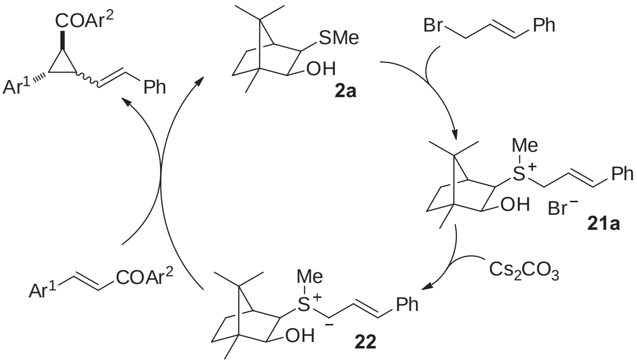
20.2.3
Cyclopropanation

Asymmetric catalytic cyclopropanation via sulfide alkylation/deprotonation has been realized by Tang, Wu, and coworkers [40]. When a mixture of chalcones (1.0 equiv), phenyl allylic bromides (1.5 equiv), and sulfonium salt *exo*-**21a** (0.2 equiv) was stirred at 0 °C in the mixed solvent of *tert*-butyl alcohol and acetonitrile, the cyclopropanation products were obtained in 66–92% yield with moderate diastereoselectivities (trans : cis up to 87 : 13) and good to high enantioselectivities (77–88% ee) (Scheme 20.19). Both *exo*-sulfonium salt **21a** and the *endo*-sulfonium salt (from **2b)** were found to catalyze the cyclopropanation of α,β-unsaturated ketones quite well, affording the desired cyclopropanes in good to high yields but with opposite asymmetric induction. Similar results were observed when sulfide was used directly instead of preformed sulfonium salts. Notably, in the corresponding stoichiometric reaction using an equimolar amount of sulfonium salts, the cyclopropanations of a broad range of β-aryl-α,β-unsaturated esters, amides, ketones, and nitriles, as well as β-alkyl-α,β-unsaturated esters and ketones, all proceeded well, giving 1,3-disubstituted-2-vinylcyclopropanes with high diastereoselectivities and enantioselectivities. Even in the cases of methyl crotonate and acrylonitrile, 98% yield and 95% ee and 50% yield and 87% ee were obtained, respectively. However, attempts to realize a catalytic reaction using methyl cinnamate or *N*,*N*-dimethylcinnamamide failed.



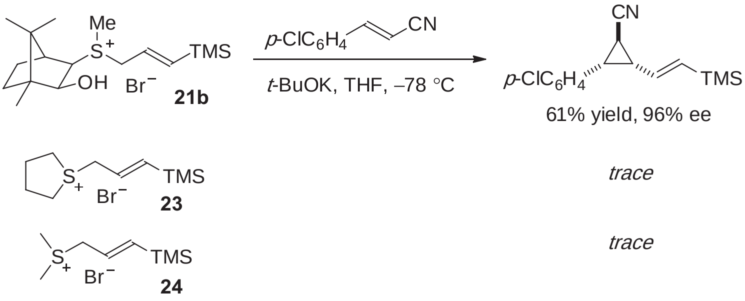
Scheme 20.19 Catalytic asymmetric cyclopropanation reactions.

A catalytic cycle was proposed as shown in Scheme 20.20. First, the sulfide **2a** reacts with cinnamyl bromide to afford the sulfonium salt **21a**, which is deprotonated by Cs_2CO_3 to generate ylide **22**. Then, the reaction of ylide **22** with α,β-unsaturated ketones give the vinyl cyclopropanes and regenerates the sulfide.



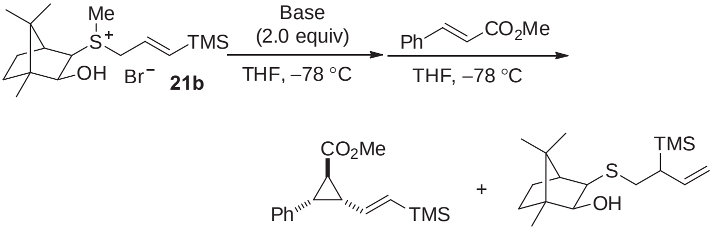
Scheme 20.20 Catalytic cycle of sulfide-mediated cyclopropanation.

The camphor-derived β-hydroxyl-sulfonium ylide proved to be unusually efficient for the cyclopropanation of electron-deficient alkenes. For example, the reaction of salt **21b** with α,β-unsaturated nitrile affords the desired cyclopropane in 61% yield and 96% ee. In comparison, the corresponding tetrahydrothiophene and dimethyl sulfide-derived sulfonium salts (**23** and **24**), which lack the hydroxyl group, only gave a trace amount of the desired cyclopropane (Scheme 20.21).



Scheme 20.21 Control experiments with different sulfonium salts.

When the hydroxyl group in sulfonium salt **21a** was methylated, no desired cyclopropane was observed in the reaction with methyl cinnamate and only rearrangement products were isolated, which resulted from the 2,3-sigmatropic rearrangement of the ylide (Scheme 20.6), indicating that the hydroxyl group play a crucial role in this reaction. The rearrangement side-reaction was also found to be base-dependent (Scheme 20.22), and weaker bases could reduce the *S*-methyl deprotonation and thus suppress the 2,3-sigmatropic rearrangement.



LDA	trace	40%
BuLi	trace	65%
t-BuOK	71%, 96% ee	trace

Scheme 20.22 Base effect on reaction yields.

A computational study revealed that the free hydroxyl group was involved as an H-bond donor in a ten-membered transition state, which can readily account for the observed stereoselectivity (Figure 20.4). The hydrogen bond formation would contribute to the reduction of the activation energy. Several transition structures without a hydrogen bond were also calculated, but higher activation energies were found. The authors found that in contrast to the epoxidation and aziridination where the reactions of sulfur ylides with aldehydes or imines occur via betaine intermediates [41], the addition transition structures in the cyclopropanation lead directly to the rapid formation of the cyclopropane and ring closure occurs without barrier. Thus, the stereochemical outcomes of the cyclopropanation are

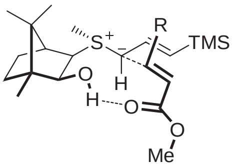
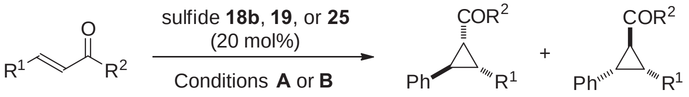
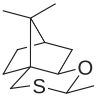


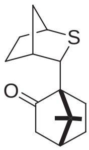
Figure 20.4 Proposed activation model in the cyclopropanation.

Table 20.3 Catalytic asymmetric cyclopropanation via carbene generation of ylides.





18b



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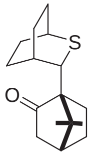

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Entry	R^1	R^2	Sulfide	Conditions[a)]	Yield (%)	d.r.[b)]	ee (%)
1	Ph	Ph	**18b**	A	38	4:1	97
2	Ph	Me	**18b**	A	14	4:1	>98
3	Ph	Ph	**19**	B	30[c)]	5:1	89
4	Ph	Ph	**25**	B	73	4:1	91
5	Ph	Me	**25**	B	5	–	–
6	Me	Ph	**25**	B	50	4:1	90
7	H	OEt	**25**	B	10	7:1	–

a) Reaction conditions: A: $PhCHN_2$ (1 equiv.), toluene, room temperature, 12 h; B: PhCHNNTsNa (1.5 equiv.), $BnEt_3NCl$ (20 mol%), dioxane, 40 °C.

b) **a** : **b**.

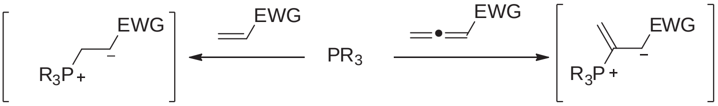
c) 50% starting material recovered.

determined by the relative stabilities of those transition structures involved in the initial C–C bond formation step.

The application of carbene generation of ylide to catalytic asymmetric cyclopropanation was reported by Aggarwal and coworkers in 1997 [42]. The sulfur ylides were generated *in situ* from the sulfide **12** and phenyl diazomethane in the presence of $Rh_2(OAc)_4$ (1 mol%) (Table 20.3, conditions A). The ylides then react with enones to give the corresponding cyclopropanes in excellent enantioselectivity and moderate diastereoselectivity (entries 1 and 2). No background cyclopropanation was observed in the absence of sulfides. Replacing phenyl diazomethane with ethyl diazoacetate only gave cyclopropanes when achiral sulfides were used in combination with $Cu(acac)_2$ as a transition-metal catalyst [43]. The major drawbacks of this method are the use of hazardous diazo compounds and the sulfide cannot be fully recovered. Later, the same group disclosed a modified procedure that utilized the *in situ* generation of the diazo compounds from tosyl hydrazone salts in the presence of a phase-transfer catalyst (Table 20.3, conditions B) [39]. Sulfide **19**, which was shown to be effective for epoxidation and aziridination (Sections 20.2.1 and 20.2.2), was not an effective cyclopropanation catalyst (entry 3), while its six-membered analog, sulfide **25** was more reactive – good yields and higher enantioselectivities were obtained for phenyl enones. Diastereoselectivities ranged from 4 : 1 to 7 : 1 for these substrates, and the sulfide could be recovered quantitatively. Methyl ketones and unsubstituted acrylates proved to be problematic under these reaction conditions (entries 5 and 7, respectively).

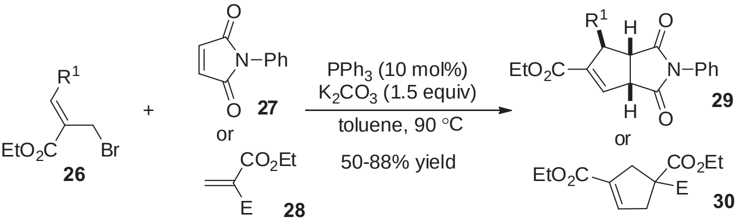
20.3
Enantioselective Phosphorus and Arsenic Ylide Catalysis

In contrast to the wide application of phosphorus ylides (e.g., Wittig reagents) in organic synthesis, the development of phosphine-catalyzed ylide reactions has lagged far behind. In the Wittig reaction, the first step is also nucleophilic attack of the ylidic carbanion to the carbonyl carbon, similar to the sulfide-catalyzed epoxidation reactions, while the release of the sulfide and phosphine proceeds in quite different ways. In the Wittig reaction, due to the high oxophilicity of the phosphorus atom, phosphine eliminates in the form of phosphine oxides to produce the alkene product, while sulfur ylide gives the epoxide product and sulfide is simultaneously regenerated. To realize a catalytic phosphorus ylide reaction with phosphine as the catalyst, the key is to find a way to regenerate the phosphines via reduction of the phosphine oxides or prevent the formation of stable four-membered intermediates (Scheme 20.1). Note that the phosphine-mediated reactions of electron-deficient olefins such as Morita–Baylis–Hillman (MBH) reactions and [3+*n*] cycloaddition of activated allenes (Scheme 20.23), in which no ylide-type of intermediates are involved, will not be described here.



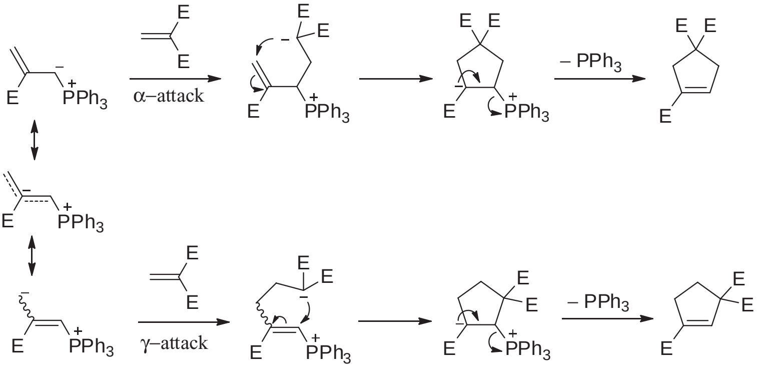
Scheme 20.23 Phosphine-mediated activation of electron-deficient alkenes and allenes.

In 2003, Lu and coworkers reported the first phosphine-catalyzed ylide reactions in an allylic ylide [3+2] annulation reaction. Allylic bromides **26** reacted with dually activated olefins **27** or **28** smoothly at 90 °C in the presence of a catalytic amount of PPh_3, affording the [3+2] cycloaddition products **29** and **30** respectively, in moderate to good yields with high diastereoselectivity (Scheme 20.24) [4d, 44].



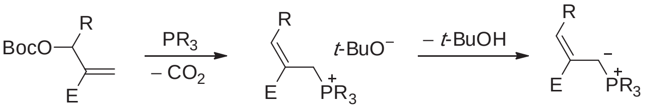
Scheme 20.24 Phosphine-catalyzed ylide annulation reaction of allylic bromide.

The authors gave the following rationalization to explain the ylide annulation (Scheme 20.25). Triphenylphosphine reacts with bromide **26** to form a phosphonium salt, which is deprotonated by K_2CO_3 to generate the corresponding phosphonium ylide *in situ*. A Michael addition of the ylide to the electron-deficient olefins, followed by another intramolecular Michael addition of the zwitterionic intermediates, and then β-elimination of triphenylphosphine completes the catalytic cycle. The formation of the two isomers can be explained by α- or γ-attack of ylide to dually activated olefins **28**. Of course, the possibility of migration of the double bond in cyclopentene products **30** under the reaction conditions cannot be excluded.



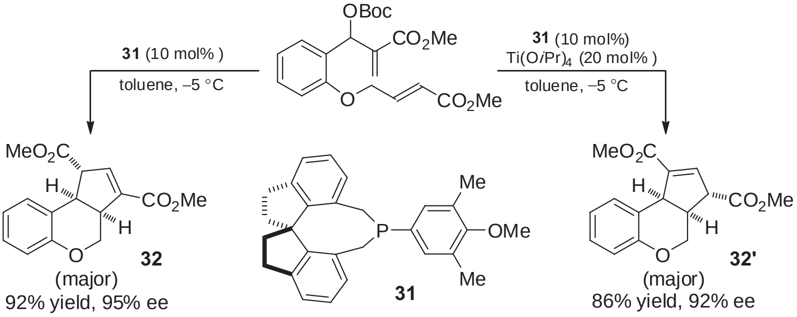
Scheme 20.25 Proposed mechanism of the phosphine-catalyzed annulation reaction.

Notably, the use of Boc-protected MBH adducts can deliver the same products as the corresponding bromides under neutral conditions without K_2CO_3 as an external base, because the *in situ* generated *tert*-butoxide anion can act as a base in the deprotonation of the phosphonium salts to afford the active ylide intermediate (Scheme 20.26).



Scheme 20.26 Generation of ylides from MBH carbonates under neutral conditions.

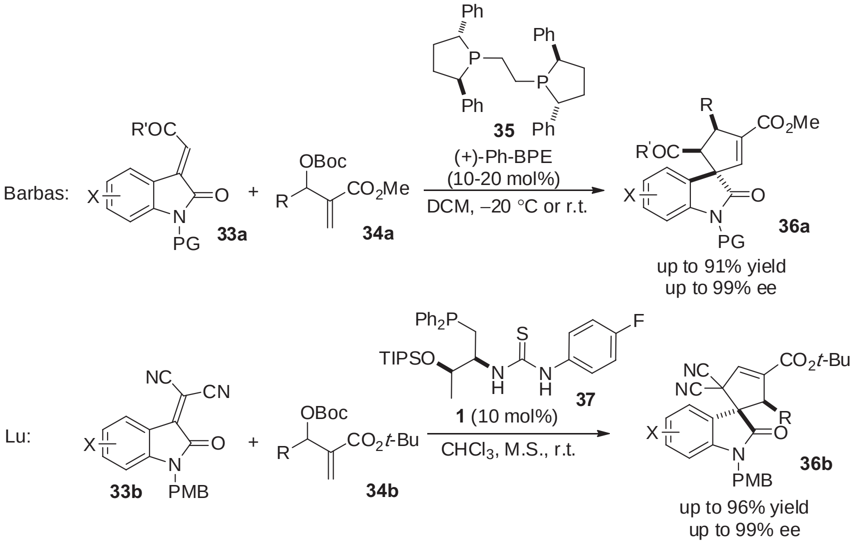
The introduction of the activated allylic bromides and Morita–Baylis–Hillman acetates and carbonates pioneered the development of a number of phosphine-catalyzed reactions in subsequent years [45]. Interestingly, the asymmetric variant of this type of transformation only appeared in the literature seven years later. In 2010, Tang, Zhou, and coworkers disclosed a highly enantioselective intramolecular ylide [3+2] annulation using spirobiindane-based phosphine catalyst **31** (Scheme 20.27). BINAP was found inactive in this reaction even at an elevated temperature (70 °C). Notably, both optically active benzobicyclo[4.3.0] compounds **32** and **32′** with three continuous stereogenic centers could be obtained as major products in high yields and stereoselectivities just by a choice of an additive [Ti(OPr^i)$_4$], which can block the isomerization of the double bond [46].



Scheme 20.27 Spiro-phosphine-catalyzed asymmetric annulation reactions.

Recently, Barbas [47] and Lu [48] independently reported phosphine-catalyzed stereoselective [3+2] cycloaddition reactions between the isatin-derived alkenes **33** and MBH carbonates **34** for the synthesis of 3-spirocyclopentene-2-oxindoles **36**, the spiro scaffold of which is found as a key structure in many natural products and drug candidates (Scheme 20.28).

Barbas *et al.* found that replacing the N-Boc group with a benzyl or amide protecting group could significantly improve the enantioselectivity, while at a lower



Scheme 20.28 Chiral phosphine-catalyzed [3+2] cyclization of alkylidene-indolinone.

temperature (–20 °C) the N-Boc protected substrates could also be converted into the desired products with excellent enantioselectivity. (*R*)-BINAP failed to promote the reaction in dichloromethane (DCM) at room temperature, which might due to its steric hindrance and weak nucleophilic ability. To account for the asymmetric induction observed, an interaction between the second phosphine moiety of the biphosphine catalyst **35** with the carbonyl of the methylene-indolinone was proposed (Figure 20.5), on the basis of ^{31}P NMR analysis and a control experiment using benzylidene-indolinone, which lacks the ester group and led to a poor stereochemical control (44% ee).

In Lu's work, the hydrogen-bonding interactions between the thiourea moiety of the bifunctional catalyst **37** and the indolinone **33b** were proposed to account

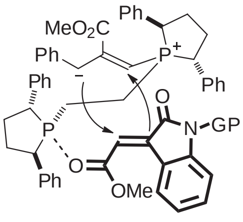


Figure 20.5 Proposed interaction between the ylide and alkylene-indolinone.

for the observed asymmetric induction. Notably, replacement of the thiourea moiety in the catalyst (TBS- rather than TIPS-protected one, see Scheme 20.28) with a urea unit resulted in a faster reaction, but with slightly decreased enantioselectivity and the thiourea catalyst containing a 3,5-di-trifluoromethylphenyl group was less effective than the 4-fluorophenyl-derived thiourea. Two regioisomers were observed due to the doubly activated double bond in the alkylideneindolinone and the two reactive sites (α,γ-carbons) in the ylide intermediate, while the N-PMB group improved the regioselectivity from 2 : 1 to 13–14 : 1 (γ : α). Only moderate enantioselectivities were observed in both studies with the alkyl MBH carbonates (R = alkyl).

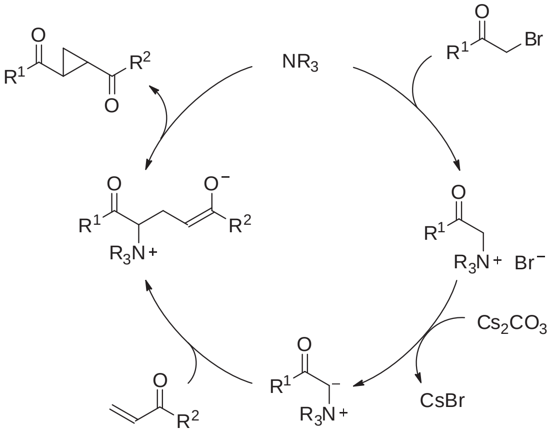
Although till now few examples of enantioselective phosphine-catalyzed ylide reactions have been reported, the potential of this kind of catalysis is apparent. In the light of the broad spectrum of readily available phosphine catalysts such as binol-derived, spiro-, and bifunctional-phosphines, which have been widely used as ligands in transition metal catalysis, together with the basis of achiral phosphine-catalyzed transformations [45], the advent of an increasing number of asymmetric reactions can be anticipated. Importantly, the phosphine-catalyzed Wittig reaction has also been realized recently, using a racemic cyclic phosphine oxide as a pre-catalyst and Ph_2SiH_2 as a reducing agent [49]. Asymmetric phosphine-catalyzed transformations based on this reduction system are promising.

So far, asymmetric arsonium ylide reactions are limited to stoichiometric transformations using preformed arsonium salts [50], which might due to the difficulty in synthesizing chiral arsine compounds [51]. Interestingly, the first example of catalytic Wittig-type reactions was realized with arsine catalysts more than 30 years ago. In 1989, Huang *et al.* found that tributylarsine could be used as the catalyst for the olefination of various aldehydes with methyl bromoacetate, employing triphenyl phosphite as a reducing agent [52].

20.4

Enantioselective Nitrogen Ylide Catalysis

Though tertiary amines can also be used to generate ylides upon reaction with an alkylating agent followed by deprotonation with a base, due to the poor leaving group ability of the ammonium there are so far only a few examples of amine-catalyzed ylide reactions [53]. Gaunt and coworkers first demonstrated the possibility of establishing a catalytic asymmetric ammonium ylide transformation by using a catalytic amount of tertiary amines (20 mol% of DBACO) in the cyclopropanation of electron-deficient alkenes with α-bromo ketones, esters, and amides. Scheme 20.29 shows the proposed catalytic cycle. The initial S_N2 reaction between the amine catalyst and the bromocarbonyl affords a quaternary ammonium salt that is deprotonated by a base to give the ammonium ylide. The presence of the carbonyl group can efficiently lower the pK_a of the adjacent protons such that they can be abstracted by a weak carbonate base. Michael addition and subsequent ring closure release the catalyst [54].

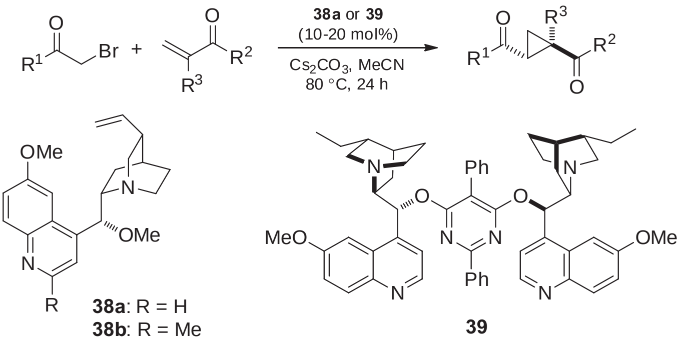


Scheme 20.29 Catalytic cycle of tertiary amine-promoted cyclopropanation.

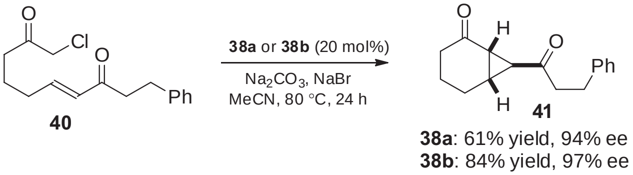
With quinine or quinidine-derived catalysts, the asymmetric cyclopropanation reaction provides a wide range of 1,2-dicarbonylcyclopropanes in good to high yields and high enantioselectivities (Table 20.4). The combination of α-bromoesters with enones was found to be more efficient than the combination of α-bromoketones with unsaturated esters. Cyclopropanation with bromomethyl alkyl ketones was problematic, giving the desired cyclopropane in low yields, while no example of β-substituted α,β-unsaturated carbonyl compounds was reported. An elevated temperature (80 °C) is necessary to ensure a good yield in an appreciable reaction time. $CsCO_3$ was more efficient than $NaCO_3$ in deprotonating the ammoniums to generate ylide intermediates. More complex amines like **39** often provide better enantioselectivity, when quinine or quinidine failed to give good results. The authors also noticed that in some cases the slow addition of reactants to a solution of the catalyst could lead to a higher yield [55].

Later, the same group disclosed an intramolecular version of this transformation, providing a facile access to [4.1.0]bicycloalkanones **41** (Scheme 20.30). Although high enantioselectivity was achieved with cinchona alkaloid-derivatives as a catalyst in their earlier study, the yields of the reaction were only moderate [56]. Mechanistic investigations revealed that the quinoline nitrogen atom (see **38a**) could be alkylated during the reaction, resulting in nonproductive ammonium salts. This problem has been readily solved by substituting the adjacent C–H with a C–Me group to block the quinolone *N*-alkylation (see **38b**) [56b]. This simple modification not only significantly improved the yields of the reactions but also slightly promoted the enantioselectivity. Remarkably, in all cases shown by the authors, only a single diastereomer was observed. Notably, the addition of NaBr can shorten the reaction time from 4 days to 1 day, and also dramatically improves the enantioselectivity from 64% to 94% ee, which might be due to suppression of the nonselective background reaction, but no explanation was given. The use of NaI as an additive gave a similar yield and enantiomeric excess as NaBr [56a].

Table 20.4 Chiral amine-catalyzed cyclopropanation of α,β-unsaturated carbonyls.

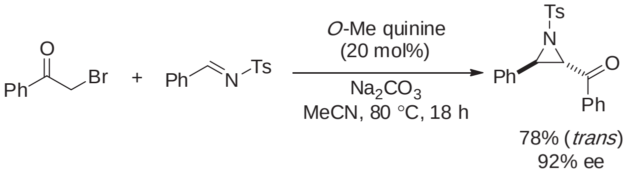


Entry	Catalyst	R^1	R^2	R^3	Yield (%)	ee (%)
1	38a	OBu^t	Ph	H	96	86
2	38a	OBu^t	4-(NEt$_2$)-C$_6$H$_4$	H	73	84
3	38a	OBu^t	4-BrC$_6$H$_4$	H	83	85
4	38a	NEt$_2$	Ph	H	94	97
5	38a	OBu^t	Ph	Me	63	92
6	38a	OBu^t	OMe	NBoc$_2$	90	97
7	38a	NMe(OMe)	C$_5$H$_{11}$	H	65	96
8	39	NMe(OMe)	4-BrC$_6$H$_4$	H	67	96



Scheme 20.30 Amine-catalyzed asymmetric intramolecular cyclopropanation.

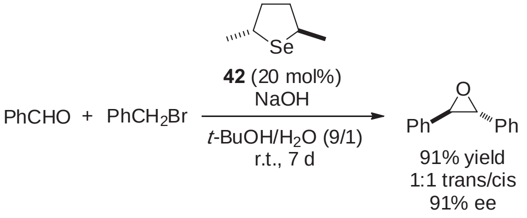
Recently, Yadav and colleagues developed a catalytic aziridination reaction of imines via ammonium ylides and disclosed an example of asymmetric transformation using *O*-methyl quinine as a catalyst. Under similar reaction conditions (Na_2CO_3, MeCN, 80 °C, 18 h) to Gaunt's, 20 mol% catalyst promoted the reaction of *N*-tosyl benzaldimine with α-bromo acetophenone with high stereoselectivity (78% yield, 92% ee) in favor of the trans product (Scheme 20.31). However, only one example was presented. The generality of this reaction needs to be explored further [57].



Scheme 20.31 Amine-catalyzed asymmetric aziridination of an imine.

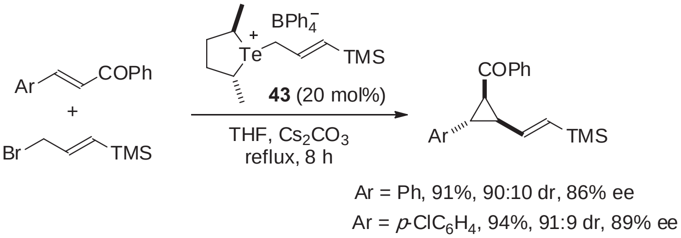
20.5
Enantioselective Selenium and Tellurium Ylide Catalysis

When compared with phosphonium and sulfonium ylides, the corresponding selenonium and telluronium ylides frequently exhibit better reactivity and nucleophilicity, while the use of selenides and tellurides in catalytic ylide reactions is far less reported. In 2001, Metzner and coworkers reported an asymmetric epoxidation reaction of aldehydes using a C_2-symmetric selenide **42** resembling their sulfide catalyst (Scheme 20.32). High yields (65–97%) and enantioselectivity (76–94% ee) were obtained with a range of aromatic aldehydes and cinnamaldehydes. However, no diastereoselectivity (trans : cis = 1 : 1) was observed in these reactions, while the corresponding sulfide gave around 80% diastereoselectivities, which could be rationalized as the formation of a less diastereoselective early transition state with the more reactive selenonium ylides. The reactions of more electron-deficient aryl aldehydes (*p*-Cl and *p*-CF_3) were less enantioselective (76% ee and 83% ee, respectively) [58].



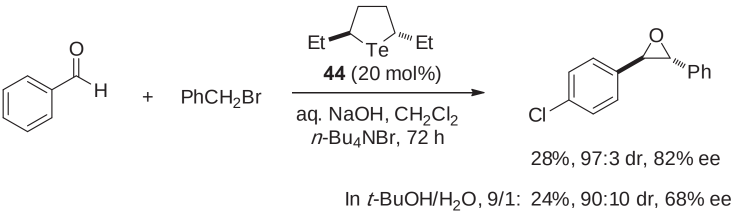
Scheme 20.32 Selenide-catalyzed asymmetric epoxidation reaction.

Achiral tellurides were used in the catalytic epoxidation of aldehydes by Huang and coworkers in 1990. With diisobutyl telluride as a catalyst (20 mol%), various aromatic, heteroaromatic, and non-primary aliphatic aldehydes can be epoxidized directly with allylic bromide to the corresponding vinyl epoxides in good yields with predominantly cis-selectivity [59]. Later, they successfully extended this method to the cyclopropanation of α,β-unsaturated ketones with allyl bromides [60]. The asymmetric version of the cyclopropanation was realized by Tang and coworkers in 2003 [61], using salt **43** directly as a catalyst (20 mol%) in the reaction of chalcones with silylated allyl bromide. The desired vinyl cyclopropanes were obtained in high yields with high diastereoselectivity and up to 89% ee (Scheme 20.33). The cyclopropanation reaction of α,β-unsaturated ketones proceeded with perfect regioselectivity, and no epoxide product was detected. With an equimolar amount of preformed telluronium salts, a broader reaction scope was achieved. Various β-alkyl, β-aryl α,β-unsaturated esters and β-aryl-α,β-unsaturated amides can be converted into the 1,3-disubstituted 2-vinylcyclopropanes with this method in high diastereo- and enantioselectivities (76–98% de, 93–99% ee). Interestingly, the diastereoselectivity can be switched by altering the base and additives (LiTMP/HMPA versus LDA/LiBr).



Scheme 20.33 Catalytic cyclopropanation with a telluronium salt.

An example of the telluride-catalyzed asymmetric epoxidation of aldehydes has been given by Metzner and coworkers, using (2*S*,5*S*)-2,5-diethyltellurolane as the catalyst. Both the enantio- and diastereoselectivity in the typical solvent system (Bu^tOH/H_2O, 9 : 1) were lower than that in dichloromethane, which gave the epoxide in 28% yield (97 : 3 dr) and 82% ee (Scheme 20.34) [58b].



Scheme 20.34 Telluride-catalyzed epoxidation reaction of benzaldehyde.

20.6
Summary and Conclusions

Highly enantioselective ylide-type covalent catalysis has been achieved with sulfides, phosphines, tertiary amines, selenides, and tellurides, and the reported reaction types include epoxidation, aziridination, cyclopropanation, and other cyclization reactions. So far, the sulfur ylide-mediated reactions are the best studied, and two ylide-generation methods (alkylation/deprotonation and carbene-transfer) have been developed. Although currently the reaction types are mainly restricted to these small-ring formations, recently the ylide-initiated tandem cyclization [4c–d, 62] has emerged as a facile and powerful approach for the synthesis of cyclic molecules – such as chromenes, cyclohexadienes, cyclohexadiene epoxides, and bicyclic compounds – beyond simple three-membered rings, representing a new trend in the ylide chemistry, but it is also a challenging task in this area to achieve highly enantioselective catalytic transformations. Moreover, phosphine-catalyzed asymmetric ylide reactions started to appear [46–48] and, importantly, the first phosphine-catalyzed Wittig reaction have been realized recently by incorporating a reduction system [49]. Overall, asymmetric catalytic ylide reactions have shown some unique features with advantages, and can be expected to be employed in a growing number of new reactions and total syntheses in the future.

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Part III

Tuning Catalyst Activity and Selectivity by the Reaction Medium and Conditions

21
"Non-Classical" Activation of Organocatalytic Reactions (Pressure, Microwave Irradiation.)

Piotr Kwiatkowski, Krzysztof Dudziński, and Dawid Łyżwa

21.1
Introduction

Over the last decade, remarkable progress has been made in the development of enantioselective catalysis using metal-free organic molecules [1]. Nowadays, organocatalysis, especially aminocatalysis, is a very powerful strategy for the asymmetric synthesis of enantiomerically enriched compounds. Moreover, in many cases this approach meets the criteria of eco-friendly and safe organic synthesis [2]. Despite many advantages of this methodology, a large group of reactions remains unusable in fine chemicals and pharmaceuticals synthesis due to their various limitations. The major drawbacks are high catalyst loading, long reaction time, narrow substrate scope, and other problems related to reactivity.

Towards solving some of these limitations, two directions are to be pursued: the first is to develop new, more efficient catalytic systems operating with low catalysts loading [3], and the second is to improve slow or difficult organocatalytic processes with existing catalysts by application of non-classical techniques [4, 5]. The use of selected techniques, for example, high pressure, can also help to force reactions that are still beyond the reach of classical organocatalysis.

In this chapter we report and analyze examples of asymmetric organocatalytic reactions under "non-classical" conditions: high pressure, microwave heating, ultrasound irradiation, and ball milling. Organocatalytic processes based on photochemical or electrochemical activation as well as applying continuous-flow reactors are not included.

21.2
Asymmetric Organocatalysis under High-Pressure Conditions

The high-pressure (HP) methodology in liquid systems has been quite well recognized as a very powerful tool in organic synthesis [6]. It is well known that the increase of hydrostatic pressure is able to accelerate chemical reactions with a negative volume of activation, which is defined as the difference between the

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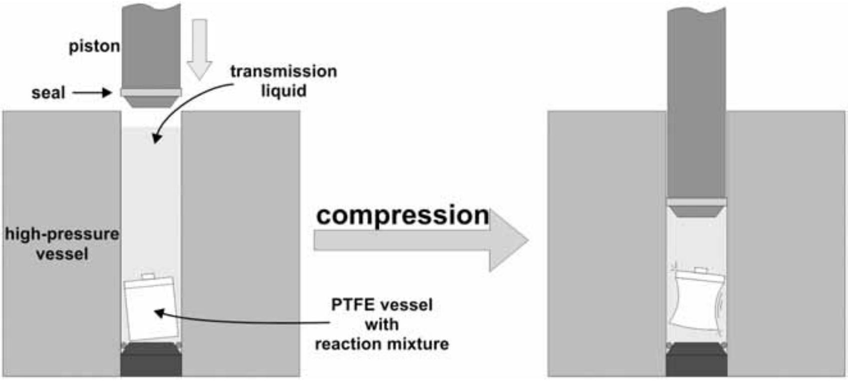


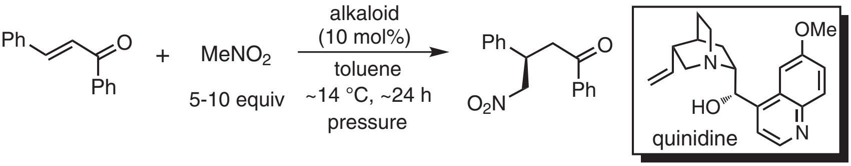
Figure 21.1 Illustration of a high-pressure experiment in a liquid system.

partial molar volume occupied by the transition state and that occupied by reactants [7]. The high-pressure technique was successfully introduced into organic synthesis by Dauben [8] in the mid-1970s, and a few years later this field was intensively explored by other groups [9]. Although this technique has found many applications in organic synthesis, asymmetric processes under high pressure are practically limited to diastereoselective reactions. Studies on catalytic enantioselective reactions with chiral organocatalysts under these conditions are still rare.

High-pressure organic reactions on a preparative scale are usually carried out in a relatively simple piston-cylinder type apparatus. A typical laboratory high-pressure apparatus with a working volume of about 50 ml is, usually, able to operate at up to 15–20 kbar. Nowadays, high-pressure equipment is commercially available even for liter-scale processes. Figure 21.1 presents the main features of such apparatus and the idea of high-pressure experiments. In this chapter the term "high pressure" refers to the range 2–20 kbar (0.2–2 GPa). Usually, organic reactions with a negative volume of activation require a pressure greater than 5 kbar to be accelerated effectively.

The influence of pressure on organic reactions catalyzed by chiral metal-free organic molecules was studied for selected asymmetric Michael, Baylis–Hillman, aldol, Mannich, Friedel–Crafts, and Diels–Alder reactions – the essential part of this work was done in Japan. In the early stages of those investigations the high-pressure technique was applied to reactions catalyzed by cinchona alkaloids and in most cases low or moderate enantioselectivities were observed. Since 2002 some examples of high-pressure reactions catalyzed by proline, thioureas, and modified cinchona alkaloids have appeared.

In 1981 Matsumoto and Uchida [10] reported the first example of an enantioselective reaction catalyzed by chiral organic molecules performed under high-pressure conditions. These Japanese scientists studied the Michael addition of nitromethane to chalcone catalyzed by cinchona alkaloids (quinine, quinidine, cinchonidine, and cinchonine), brucine, and strychnine. The authors did not observe product formation under atmospheric pressure with cinchona alkaloids in aprotic solvents; however, the reaction is possible in methanol (<1% ee) [11]. More recently, another group investigated this reaction with quinidine (10 mol%) at 80 °C in 1,2-dichloroethane, and after two days the product was obtained with only 13% yield and 33% ee [12]. Under high-pressure conditions (10 kbar) and with cinchona alkaloids Matsumoto obtained the product with very high yields (87–100%) and low or moderate enantioselectivity. The best results in terms of enantioselectivity (51% ee) were observed in toluene with the alkaloid quinidine (Scheme 21.1 and Table 21.1).



Scheme 21.1 High-pressure conjugate addition of nitromethane to chalcone.

Table 21.1 Results for the high-pressure conjugate addition of nitromethane to chalcone (Scheme 21.1).

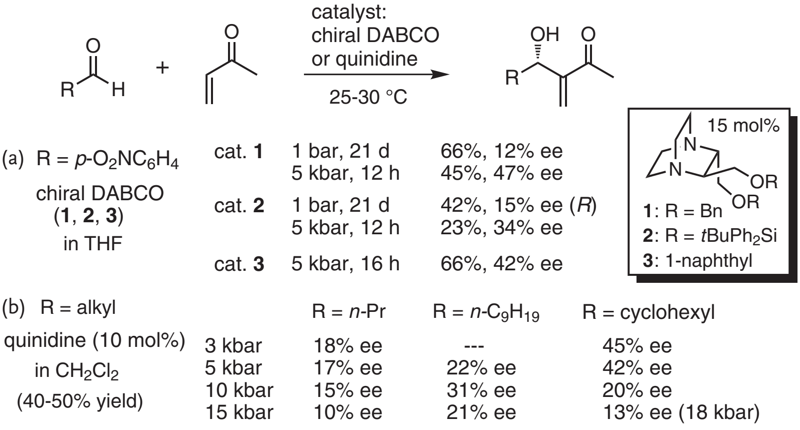
Pressure (kbar)	Quinine (10 mol%)		Quinidine (10 mol%)	
	Yield (%)	ee (%)	Yield (%)	ee (%)
0.001	0	–	–	–
4	33	35	36	58
6	51	31	81	59
9	100	27	**100**	60
10 [10]	100	24	100	51 (*R*)
15	100	23	100	53

Seven years after the work of Matsumoto and Uchida, Sera and Matsumoto [13] published extended studies on the high-pressure asymmetric Michael additions of nitromethane, thiols, and 1,3-ketoester to enones catalyzed by quinine and quinidine. The reaction of chalcone with nitromethane was investigated in more detail under different pressures (Scheme 21.1). The increase of pressure resulted in higher chemical yields. When quinine was employed as catalyst the enantioselectivity decreased at higher pressure (from 35 to 23% ee). With quinidine the enantioselectivity was on a very similar level (58–60% ee) in the pressure range 4–9 kbar and decreased slightly at 15 kbar. This example proved that high pressure can increase remarkably the reaction rate while having practically no affect on the enantioselectivity.

Other examples presented in this publication were less optimistic. The authors also investigated an addition of thiophenols to cyclohex-2-enone and 6,6-dimethylcyclohex-2-enone under a pressure of 9 kbar, even though in this case the reaction also takes place with good chemical yield at ambient conditions [14]. All reactions gave the corresponding thiophenol adducts in nearly quantitative yields and in all cases the high pressure decreased the enantioselectivity (e.g., from 39% to 26% ee in the reaction of cyclohex-2-enone and thiophenol catalyzed by quinine). A similar effect under higher pressure was observed in the reaction of methyl 1-oxoindan-2-carboxylate with methyl vinyl ketone (MVK) in the presence of quinine (51% ee at 1 bar and 44% ee at 9 kbar).

In the 1990s, examples of high-pressure Baylis–Hillman reactions catalyzed by chiral tertiary amines appeared in the literature [15–17]. In 1991 Isaacs' group [15] reported a few results of the reaction between acrylonitrile and acetaldehyde with different chiral amines under 5–9 kbar: quinine (0%), (1*R*,2*S*)-*N*-methylephedrine (18%, 10% ee), (*S*)-(–)-nicotine (15%, 11% ee), (*S*)-(–)-1-methylpyrrolidenylmethanol (28%, 17% ee), and (±)-3-hydroxyquinuclidine in ethyl L-(+)-lactate (81%, 3% ee). In general, for this reaction the combination of chiral amines and pressure resulted in low yields and enantioselectivities up to 17%.

In 1995 Hirama and coworkers [16] reported an asymmetric Baylis–Hillman reaction catalyzed by chiral 2,3-disubstituted DABCO derivatives under increased pressure (Scheme 21.2a). Hirama observed an enhancement of both reaction rate and enantioselectivity for the reaction of 4-nitrobenzaldehyde with MVK under 5 kbar. At atmospheric pressure the reaction proceed very slowly (3 weeks) with low enantioselectivity (12–15% ee). The best results in terms of yield and enantioselectivity (up to 47%) were obtained with chiral DABCO catalyst bearing benzyl or 1-naphthyl groups. This is the first example of an organocatalytic reaction demonstrating that an increase in pressure can significantly enhance the enantioselectivity (e.g., from 12% to 47%).



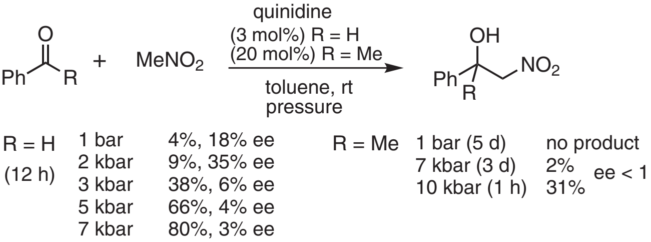
(a) R = p-O$_2$NC$_6$H$_4$ chiral DABCO (**1**, **2**, **3**) in THF			
	cat. **1**	1 bar, 21 d	66%, 12% ee
		5 kbar, 12 h	45%, 47% ee
	cat. **2**	1 bar, 21 d	42%, 15% ee (*R*)
		5 kbar, 12 h	23%, 34% ee
	cat. **3**	5 kbar, 16 h	66%, 42% ee

(b) R = alkyl		R = n-Pr	R = n-C$_9$H$_{19}$	R = cyclohexyl
quinidine (10 mol%)	3 kbar	18% ee	---	45% ee
in CH$_2$Cl$_2$	5 kbar	17% ee	22% ee	42% ee
(40-50% yield)	10 kbar	15% ee	31% ee	20% ee
	15 kbar	10% ee	21% ee	13% ee (18 kbar)

Scheme 21.2 Asymmetric Baylis–Hillman reactions with MVK and aldehydes.

A few years later Marco [17] investigated the Baylis–Hillman reaction of MVK with aliphatic aldehydes (e.g., cyclohexanecarboxaldehyde) under 10–11 kbar with cinchona alkaloids, *N*-methylprolinol, and *N*-methylephedrine (Scheme 21.2b). The highest enantioselectivity was observed with cinchonine and quinidine (25–27% ee). Finally, quinidine was employed to study the influence of pressure (3–18 kbar) on the enantioselectivity of the reaction of MVK with aliphatic aldehydes (Scheme 21.2b). The general conclusion was that the use of higher pressure resulted in a decrease in enantioselectivity (e.g., for cyclohexanecarboxaldehyde from 45% ee at 3 kbar to 13% ee at 18 kbar). Surprisingly, only for *n*-decanal was the enantioselectivity higher at 10 kbar (31% ee) than at 5 kbar (22% ee).

More than 20 years after the pioneering work on the enantioselective high-pressure Michael reaction with cinchona alkaloids [10], Matsumoto's group reported studies on the Henry reaction catalyzed by quinidine [18]. The investigations focused on the reaction of benzaldehyde with nitromethane in the range 1 bar – 7 kbar (Scheme 21.3). The reaction with quinidine in toluene is very slow under ambient conditions and the use of higher pressure accelerates the process. Unfortunately, application more than 2 kbar resulted in a significant drop of enantioselectivity.

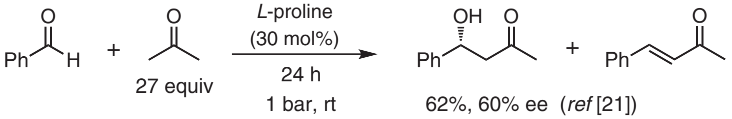


Scheme 21.3 High-pressure organocatalytic Henry reaction.

The asymmetric reaction of nitromethane with aldehydes as well as activated ketones (e.g., trifluoroacetophenone and α-ketoesters) is possible with various chiral metallic complexes or organocatalysts under atmospheric pressure with good yield and enantioselectivity. However, the Henry reaction of aryl alkyl ketones still remains problematic and challenging. Matsumoto's group also tested the very difficult reaction of acetophenone and nitromethane with quinidine. No product was observed under 1 bar and only traces at 7 kbar, but application of 10 kbar resulted in a significant improvement in yield (31%) – unfortunately, no enantioselectivity was detected (Scheme 21.3).

Examples of high-pressure organocatalytic reactions published after 2002 showed that the attention of researchers has switched to other catalytic systems that are well known as being very efficient in selected reactions under classical conditions (e.g., proline and other secondary amines as well as primary amines and thioureas). The influence of pressure on the asymmetric enamine catalysis was independently investigated by Kotsuki [19] and Hayashi [20]; however, the method of pressure generation used by each group was different. In Kotsuki’s group the pressure reactions were performed in a typical piston-cylinder type apparatus. Hayashi, though, used a very interesting method of pressure generation simply by freezing water (at −20 °C) in a sealed autoclave. Because the volume of water increases by about 10% while freezing, pressures of up to 2 kbar can be easy obtained in an autoclave at −20 °C.

In 2003 Kotsuki [19] reported studies on high-pressure promoted direct asymmetric aldol reactions between ketones and aldehydes catalyzed by L-proline (30 mol%; without DMSO). The reaction of benzaldehyde in acetone was investigated in the range 2–8 kbar at room temperature (Scheme 21.4). Only 2 kbar pressure was sufficient to obtain the product with very good yield (90%) with some improvement in enantioselectivity (72% ee) compared with the results of List and Barbas [21] (62%, 60% ee). Unfortunately, there is no information about any high-pressure reaction with a lower loading of the catalyst. The increase of pressure in this reaction resulted in decreased enantioselectivity (e.g., 63% ee at 8 kbar).

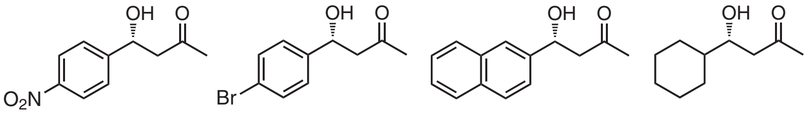


	1 bar, rt	62%, 60% ee	(*ref* [21])
Kotsuki (in acetone)	2 kbar, rt	90%, 72% ee	3%
	5 kbar, rt	90%, 64% ee	
	8 kbar, rt	88%, 63% ee	
Hayashi (in DMSO)	1 bar, 23 °C	62%, 69% ee	28%
	1 bar, -20 °C	40%, 78% ee	8%
	2 kbar, -20 °C	78%, 75% ee	15%

Scheme 21.4 High-pressure organocatalytic aldol reaction.

In the same year Hayashi [20] reported a very successful high-pressure, induced by water-freezing, direct asymmetric three-component List–Barbas–Mannich reaction catalyzed by L-proline. One year later Hayashi used a similar approach for the aldol reaction (Scheme 21.4) [22]. The use of ca. 2 kbar pressure at −20 °C for the L-proline catalyzed aldol reaction between benzaldehyde and acetone (27 equiv) in DMSO gave the product in 78% yield and 75% ee. The control experiment at −20 °C and atmospheric pressure provided the aldol product with considerably lower yield (40%) and similar enantioselectivity.

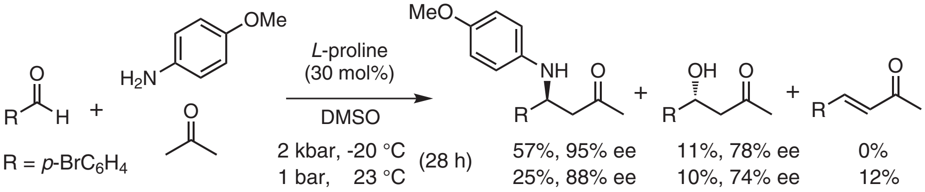
To better evaluate both methods the results of the direct aldol reaction of acetone with selected aromatic aldehydes catalyzed by proline are presented in Figure 21.2. Although in general the Kotsuki approach offers much better yields, in the Hayashi method higher enantioselectivities (temperature effect) can be obtained. This methodology was also tested in a solvent-free aldol reaction with cyclopentanone but no improvement was noticed [23].



2 kbar, rt:	89%, 64% ee	89%, 70% ee	95%, 70% ee	84%, 92% ee
1 bar, 23 °C:	63%, 69% ee	53%, 70% ee	51%, 74% ee	46%, 88% ee
2 kbar, -20 °C:	75%, 75% ee	65%, 75% ee	67%, 80% ee	21%, 96% ee
1 bar, -20 °C:	57%, 75% ee	41%, 76% ee	32%, 82% ee	6%, 90% ee

Figure 21.2 Comparison of classical and high-pressure L-proline catalyzed direct aldol reactions.

As already mentioned, a very high positive effect of pressure on the asymmetric organocatalytic Mannich-type reaction catalyzed by proline was observed by Hayashi (Scheme 21.5 and Table 21.2) [20].



Scheme 21.5 Organocatalytic Mannich reaction under high pressure induced by water-freezing.

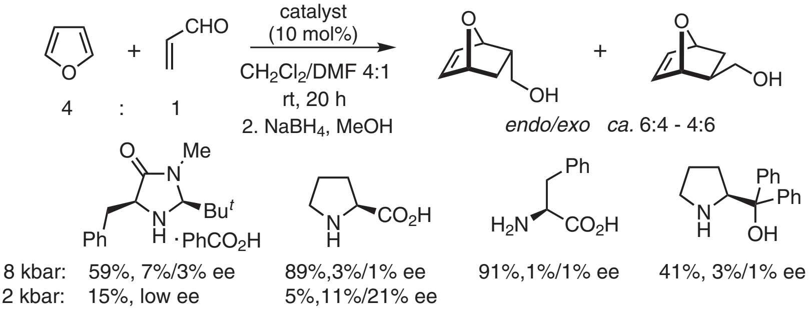
Table 21.2 Results for the organocatalytic Mannich reaction under high pressure (Scheme 21.5).

R	Time (h)	Mannich product			
		2 kbar, –20 °C		1 bar, 23 °C	
		Yield (%)	ee (%)	Yield (%)	ee (%)
Ph	72	99[a)]	93	12[a)]	79
p-$O_2NC_6H_4$	12	58	91	20 (5)[b)]	90 (98)[b)]
p-$MeOC_6H_4$	96	99[a)]	94	0[a)]	–
1-Naphthyl	48	67	93	14	86
3,4-Di(MeO)C_6H_3	96	65[a)]	95	0[a)]	–
p-$AcHNC_6H_4$	24	82	92	0	–
2-Furyl	41	95	>99	65	95
Cyclohexyl	40	90	84	23	4

a) Yield after reduction with $LiAlH_4$.
b) 1 bar, –20 °C.

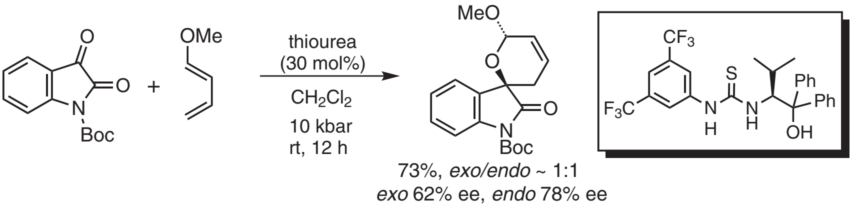
The reaction of acetone, 4-bromobenzaldehyde, and 4-anisidine under high pressure induced by water freezing afforded the Mannich adduct with 57% yield and very high enantioselectivity (95% ee). The same reaction under ambient conditions proceeds slowly, with 25% yield and lower enantioselectivity (88% ee). In addition, relatively high amounts of the side aldol product (10%) and enone (12%) were obtained. To demonstrate the scope of the method other aldehydes were applied in the high-pressure Mannich reaction. The most impressive results were obtained under 2 kbar with aromatic electron-rich aldehydes, for example, *p*-anisaldehyde, 3,4-dimethoxybenzaldehyde, and 4-acetamidobenzaldehyde (65–99% yield, 92–97% ee). Using the conventional approach (1 bar, room temperature) no product was detected for these aldehydes! For the simple benzaldehyde the pressure method also remarkably changed the reaction profile (12% and 79% ee versus 99% and 93% ee). Finally, a very high increase in yield and enantioselectivity was observed for aliphatic cyclohexanecarboxaldehyde (from 23% and 4% ee to 90% and 84% ee). In this case, the difference in enantioselectivity is very high (80 percentage points!), but it is difficult to conclude if it is only a matter of the temperature effect or if the pressure also takes part in this phenomenon (no data for −20 °C at 1 bar). Based on the results with *p*-nitrobenzaldehyde at −20 °C at 2 kbar (91% ee) and 1 bar (98% ee) the authors suggested that the pressure reduces the enantioselectivity. In conclusion, the high pressure induced by water freezing in three-component Mannich reaction prevents formation of by-products, extends the substrate scope, and provides higher yields and enantioselectivities than the conventional method at room temperature and pressure of 1 bar.

In 2010 Kotsuki [24] reported high-pressure studies on a difficult Diels–Alder reaction of furan and acrolein catalyzed by secondary and primary amines, for example, proline, phenylalanine, diphenylprolinol, and the MacMillan catalyst (Scheme 21.6). The best results in terms of yield were obtained with simple amino acids (proline and phenylalanine) under 8 kbar but, unfortunately, were accompanied with very low ee. The use of lower pressure (2 kbar) and proline as a catalyst resulted in very low yield and an increase in enantioselectivity up to 21%.



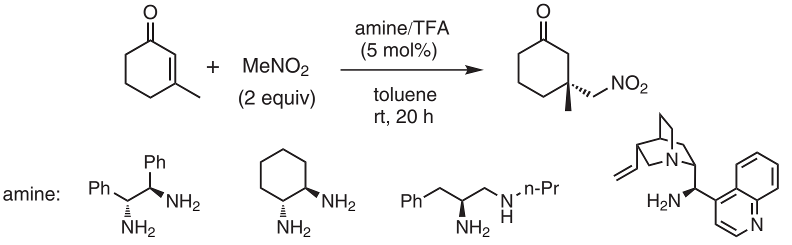
Scheme 21.6 Organocatalytic high-pressure Diels–Alder reaction of furan with acrolein.

The same group investigated the high-pressure organocatalytic asymmetric hetero-Diels–Alder (HDA) reaction of *N*-protected isatins with electron-rich dienes (1-methoxybutadiene and Danishefsky's diene) catalyzed by chiral thioureas [25]. Other activated ketones, especially α-ketoesters, were also applied to the HDA reaction catalyzed by achiral thioureas under high pressure [26]. The reaction of *N*-Boc-isatin with 1-methoxybutadiene was chosen for screening chiral organocatalysts at 10 kbar (Scheme 21.7). Hydrostatic pressure accelerates the HDA reaction and the best results were obtained in dichloromethane using chiral thiourea derived from diphenylvalinol (73%, up to 78% ee). This cycloaddition reaction was extended to various *N*-protected isatins with 1-methoxybutadiene (71–91%, 28–67% ee) as well as the Danishefsky's diene (38–47%, 34% ee).



Scheme 21.7 Organocatalytic high-pressure hetero-Diels–Alder reaction of isatins.

In 2011 Kwiatkowski and coworkers [27] reported a significant effect of hydrostatic pressure on the difficult organocatalytic 1,4-conjugate addition of nitroalkanes to prochiral sterically congested β,β-disubstituted enones. Various chiral primary amines were tested with TFA as a co-catalyst in the model reaction of 3-methylcyclohexenone and 2 equivalents of nitromethane (Scheme 21.8). Catalyst screening under ambient conditions revealed a very low conversion of 3-methylcyclohexenone. In contrast, application of a pressure of 10 kbar and a catalytic amount of 1,2-diamines accelerated remarkably the reaction rate. In some



10 kbar	55% (60%) 98% ee	55% (95%) 75% ee	70% (77%) 82% ee (*S*)	78% (91%) 96% ee	75% (99%) 98% ee
1 bar	2%	6%, 83% ee	9%, 80% ee	1%	3%

(conversion in parentheses)

Scheme 21.8 Michael reaction of 3-methylcyclohexenone with nitromethane.

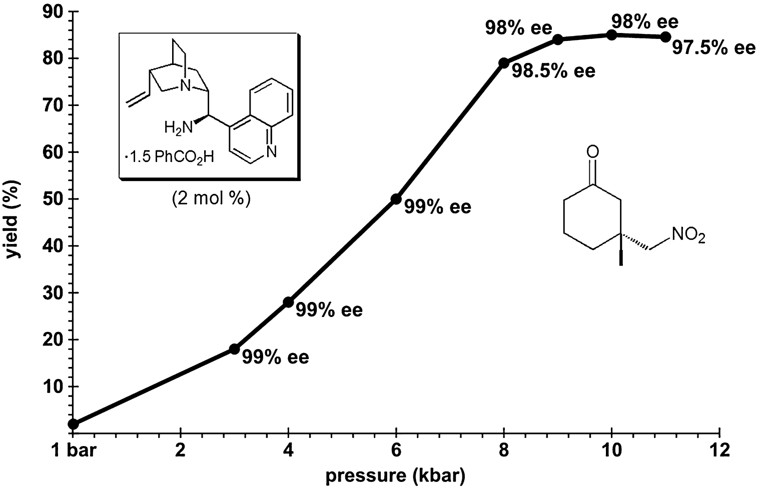


Figure 21.3 Pressure effect on the Michael reaction of 3-methylcyclohexenone with $MeNO_2$.

cases a moderate yield and very high conversion was observed because of subsequent Henry reaction with excess of nitromethane. The highest efficiency in terms of yield and enantioselectivity was achieved with easily accessible 9-amino-9-deoxy-*epi*-cinchonine. Replacement of the TFA co-catalyst with benzoic acid and reduction of the reaction time to 5 h improved the yield and enantioselectivity to 87% and 98% ee. This reaction is also efficient with 1 mol% of the catalyst after 20 h (84%, 98% ee).

Figure 21.3 illustrates the significant effect of pressure increase on the reaction rate with 2 mol% of the catalyst after 20 h. Most importantly, the pressure in the range 3–10 kbar has practically no affect on enantioselectivity (98.5 ± 0.5% ee) in this reaction.

This approach also allows a very efficient synthesis of different γ-nitroketones containing quaternary stereogenic centers starting from cyclic as well as selected acyclic β,β-disubstituted enones and cinchonine-based primary amine catalyst (Figure 21.4). The reaction is also possible with more demanding 2-nitropropane and nitroethane. In most cases, under 10 kbar pressure and in the presence of 1–5 mol% of the simple chiral primary amine catalyst, good yields and good to excellent enantioselectivities were obtained.

The high-pressure technique was also successfully applied to the asymmetric organocatalytic Friedel–Crafts alkylation of indoles with enones with the same catalytic system [28]. Alkylation of indole with benzylideneacetone was studied as a model reaction (Figure 21.5a). This particular reaction was investigated by Chen [29] (72%, 65% ee at 0 °C for 3 days) and Melchiorre [30] (90%, 88% ee at 70 °C for 1 day) under atmospheric pressure. The reaction requires a high loading of primary amines derived from cinchona alkaloids (30–20 mol%) with 2 equivalents of TfOH [29] or D-*N*-Boc-phenylglycine [30] as a co-catalyst. In high-pressure studies [28] a

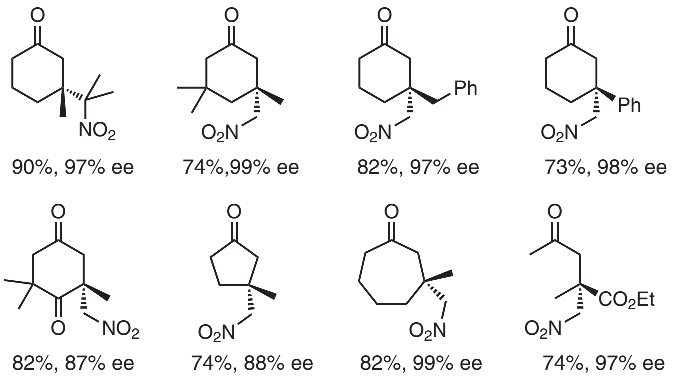


Figure 21.4 Products of organocatalytic high-pressure Michael reactions.

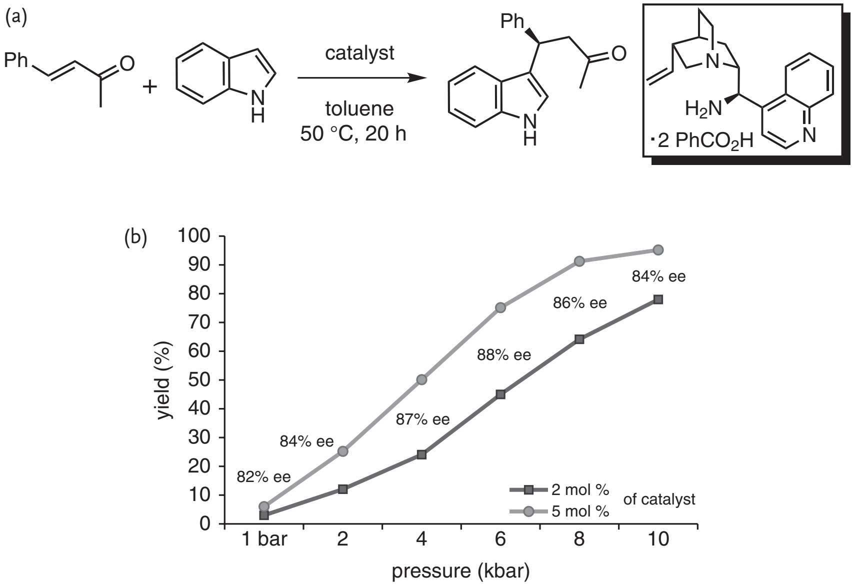
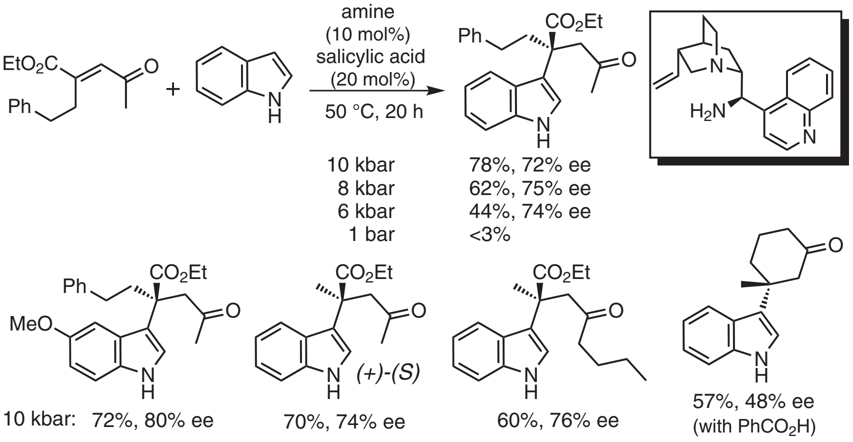


Figure 21.5 Pressure effect in the Friedel–Crafts alkylation of indole with benzylideneacetone.

less active catalyst with a similar amine and benzoic acid was applied (5–2 mol%). Figure 21.5b indicates a significant effect of hydrostatic pressure on the model organocatalytic Friedel–Crafts reaction. Under 6 kbar the highest enantioselectivity was observed (increase from 82 to 88% ee). Application of higher pressures (8–10 kbar) improved the reaction yield (64–95%) but slightly decreased the enantioselectivity (83–84% ee at 10 kbar). The use of a stronger acid additive (e.g., salicylic acid) increased the catalyst activity in this reaction but resulted in lower enantioselectivity. When only 0.5 mol% of 9-amino-9-deoxy-*epi*-cinchonine with 1.5 mol% of salicylic acid was applied under 10 kbar the product was obtained with 74% yield and 71% ee.

In this work special attention was paid to more difficult reactions of indoles with various β,β-disubstituted enones, enabling the generation of quaternary stereogenic centers. The use of the high-pressure technique promotes the organocatalytic reaction of β,β-disubstituted (*E*)-enones having an alkyl and a carboalkoxy group at the β-position with indoles. In this case good yields and enantioselectivities of up to 80% were obtained (Scheme 21.9). Surprisingly reactions with β-substituted cyclic enones are less efficient and by-product formation via subsequent addition of indole to the carbonyl group was observed.



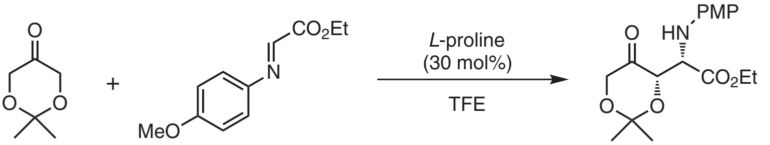
Scheme 21.9 High-pressure Friedel–Crafts reaction of β,β-disubstituted enones with indoles.

To conclude this part, in the presented investigations hydrostatic pressure (2–18 kbar) usually significantly increases the reaction rate; however, the influence on enantioselectivity is less predictable. In many discussed reactions the high pressure, unfortunately, decreases the enantioselectivity. There are, though, also some positive examples of an enantioselectivity increase, for example, in the Baylis–Hillman reaction catalyzed by chiral DABCO derivatives. Moreover, a very successful application of the high-pressure technique in terms of yield and high enantioselectivity was demonstrated for the Mannich reaction under 2 kbar [20] and recently in the Michael and Friedel–Crafts reactions of enones catalyzed by primary amines under ca. 10 kbar [27, 28]. In these reactions an increase in pressure had a somewhat negligible effect on the enantioselectivity. In our opinion the high-pressure technique is a very promising method that can be successfully used to increase the efficiency of selected asymmetric organocatalytic reactions in a highly enantioselective manner.

21.3
Asymmetric Organocatalysis under Microwave Irradiation – Thermal Effect

Microwave (MW) irradiation is the most popular non-conventional method of accelerating organic reactions, used also as an alternative to conventional heating. Over recent years, the number of publications containing microwave-assisted organic synthesis (MAOS) has increased significantly [31]. In addition, much easier access to high-performance microwave reactors compared with, for example, high-pressure equipment stimulates the fast progress in this field. The main advantage of MW irradiation is the efficient conversion of electromagnetic energy into heat, and its direct interactions with the reagents in the vessel, in contrast to the classical heating. This technique is able to significantly reduce the reaction time without decreasing the yield and also saves energy. The use of microwave irradiation to accelerate asymmetric organocatalytic reactions is still not very popular [5]. In general this technique could be useful for organocatalytic reactions that retain a high-level of enantioselectivity with increasing temperature.

The first asymmetric organocatalytic reactions conducted under microwave irradiation were described by Westermann and Neuhaus [32] in 2005. They studied a Mannich-type reaction between acetonide of dihydroxyacetone and an imine derived from ethyl glyoxylate in the presence of L-proline in trifluoroethanol (TFE) as solvent (Scheme 21.10). The reaction at room temperature with 5–30 mol% of the catalyst led, after 20 h, to the adduct with good yields (68–75%) and enantioselectivities in the range 91–99% ee. The authors discovered that the application of microwaves (300 W) accelerates this reaction, and after only 10 min the product was obtained with comparable yield (72%) and very high enantioselectivity (94% ee). However, the influence of conventional heating was not investigated for this reaction.



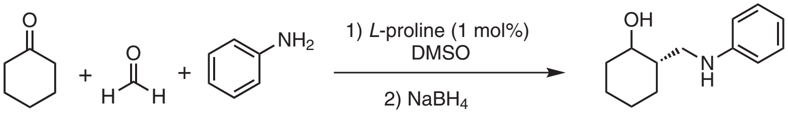
Westermann:	MW (100W), 10 min:	64%, 9:1 dr, 95% ee
	MW (300W), 10 min:	72%, 9:1 dr, 94% ee
	no MW (rt, 20 h):	72%, 97:3 dr, 99% ee
Kappe:	MW (1W), 60 °C, 20 min:	55-58%, 9:1 dr, >99% ee
	MW (83W)*, 60 °C, 20 min:	
	oil bath (60 °C) 20 min:	

* - liquid cooling

Scheme 21.10 Microwave-assisted L-proline catalyzed Mannich reaction.

A year later Rodriguez and Bolm [33] reported the asymmetric direct Mannich reaction with cyclohexanone, formaldehyde, and aniline using only 1 mol% of L-proline as catalyst (Scheme 21.11). After carrying out the reaction at 45–50 °C for 23 h and a subsequent reduction the corresponding aminoalcohol was obtained in

82% yield and 97% ee. The temperature tolerance for this reaction, as well as Westermann's [32] studies, encouraged Rodriguez and Bolm to explore the effect of microwaves. After 4 h irradiation at 48 °C (with air cooling) the yield of the desired product increased (89% versus 82%) but no change in the enantioselectivity (97% ee) was observed. In this case, comparative studies using oil bath heating were performed over a wide temperature range. The reaction was very efficient even at higher temperature (75 °C) in terms of yield and enantioselectivity. As expected, higher temperatures resulted in a faster reaction; however, to achieve comparable yields with the microwave method a longer reaction time was required. Finally, the authors concluded that no specific MW effect was observed.

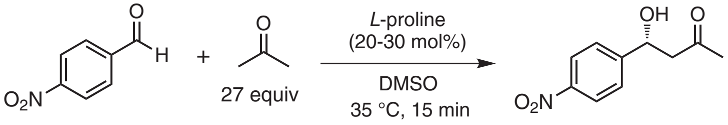


	Conditions	Result
Bolm:	MW (15W)*, 48 °C, 4 h:	89%, 97% ee
	oil bath (45-50 °C) 23 h:	82%, 97% ee
	oil bath (64-66 °C) 4-8 h:	55-68%, 98% ee
	oil bath (75-77 °C) 6 h:	84%, 98% ee
Kappe:	MW (7W), 65 °C, 5 h:	83%, 97% ee
	MW (232W)**, 65 °C, 5 h:	81%, 97% ee
	oil bath (65 °C) 5 h:	79%, 97% ee

* - air cooling
** - liquid cooling

Scheme 21.11 One-pot three-component Mannich reaction catalyzed by L-proline.

In the same year Mossé and Alexakis [34] reported microwave-assisted asymmetric aldol reactions of acetone and various aromatic aldehydes catalyzed by proline (Scheme 21.12). In the model reaction, under microwave irradiation with simultaneous air-cooling (25 °C) after 15 min the aldol product was obtained in 68% yield and with moderate enantioselectivity (74% ee). In comparison, the reaction without MW required 4 h at room temperature to afford the same yield and selectivity. Comparing the yields and enantioselectivities of the product obtained



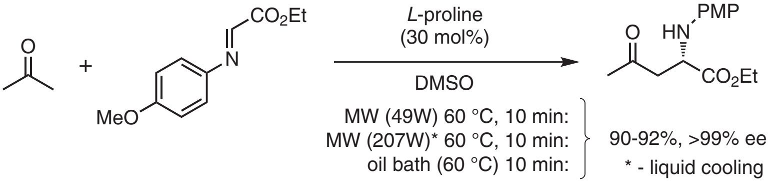
	Conditions	Result
Alexakis:	MW (15W)*:	69%, 70% ee
	oil bath:	42%, 62% ee
	MW (10W)*, 25 °C:	68%, 74% ee
	rt, 4 h:	68%, 76% ee
Kappe:	MW (2W):	62%, 69% ee
	MW (114W)**:	62%, 68% ee
	oil bath:	63%, 68% ee

* - air cooling
** - liquid cooling

Scheme 21.12 Microwave-assisted asymmetric aldol reaction.

using conventional heating versus the microwave irradiation after 15 min at 35 °C proved the superiority of the non-conventional method (42% versus 69%, 62% ee versus 70% ee). Finally, under optimal conditions, using MW irradiation, other aromatic aldehydes were also examined (38–70%, 64–70% ee).

In 2007 a very important article was published by Kappe [35], a well-known specialist in the field of the microwave research. His group re-examined the Mannich and aldol reactions presented above and carefully investigated the differences between conventional and microwave heating (results presented in Schemes 21.10–21.12). Moreover, the Mannich reaction of acetone with the PMP-protected imino ester of ethyl glyoxylate was studied (Scheme 21.13). In this case the obtained results, under MW (49 W or 270 W with liquid cooling) at 60 °C for 10 min, were very similar in terms of yield and enantioselectivity to those obtained for the reaction performed in an oil bath at the same temperature and reaction time (90–92%, >99% ee). Similar results with microwave dielectric heating and conventional thermal heating were also obtained for the Mannich and aldol reactions presented in Schemes 21.10–21.12 [35].

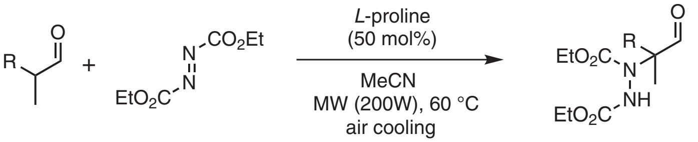


Scheme 21.13 Microwave-assisted L-proline catalyzed Mannich reaction.

The microwave irradiation was generated using a reactor setup that allowed accurate measurements of internal reaction temperature using fiber-optic probes. Experiments were carried out under at least two different power values, and also with simultaneous external cooling when a higher power of microwave radiation was applied. The same method of temperature measurement was also used in experiments with conventional heating.

In conclusion, Kappe's group demonstrated the absence of any differences between conventional and microwave heating in proline-catalyzed Mannich and aldol reactions as well as no evidence for specific or non-thermal microwave effects. In all cases, in contrast to the previous literature reports, the results obtained with microwave irradiation could be reproduced by conventional heating at the same reaction temperature and time in an oil bath. The differences observed in previous publications could be a result of incorrect temperature measurements [36]. After Kappe's [35] publication several articles appeared in the literature concerning the application of microwaves in asymmetric organocatalysis, mostly in aldol and Michael type reactions operating via enamine as well as iminium catalysis.

In 2008 Bräse’s [37] group revealed a thermally accelerated organocatalytic α-amination of α-branched aldehydes with azodicarboxylates under microwave irradiation (Scheme 21.14). Proline proved to be the best catalyst among various tested chiral secondary amines. The reaction is very slow at room temperature (2–5 days) and requires very high (50 mol%) catalyst loading. The authors found that a higher temperature significantly accelerates the reaction rate as well as increases the enantioselectivity. The model reaction resulted in 62% yield and 80% ee after 3 days under ambient conditions, but at 60 °C after only 1 h the product was formed with 79% yield and 90% ee. The application of microwave irradiation (200 W) at 60 °C reduced the reaction time to a 0.5 h and improved the yield to 97%, with 89% ee. This procedure was used for amination of different α-aryl-propionaldehydes with good to high yields and up to 90% ee. Unfortunately, a very high loading of proline (50%) was still required. In conclusion, in comparison to classical conditions, the microwave method allowed a significant reduction of reaction time from 2–5 days at room temperature to 30 min, and in many cases also improved the enantioselectivity.



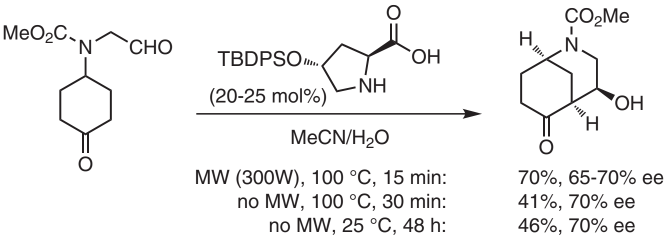
R = Ph		
	MW, 60 °C, 1 h	99%, 84% ee
	MW, 60 °C, 0.5 h	97%, 89% ee
	oil bath (60 °C) 1 h	79%, 90% ee
	oil bath (60 °C) 6 h	93%, 88% ee
	rt, 3d	62%, 80% ee

	R = 2-naphthyl	*p*-MeO-C_6H_4	*p*-F-C_6H_4	*p*-CF_3-C_6H_4
MW, 60 °C, 0.5 h:	76%, 90% ee	85%, 88% ee	91%, 89% ee	63%, 56% ee
rt, 2-5 d:	54%, 84% ee	85%, 75% ee	26%, 68% ee	19%, 24% ee

Scheme 21.14 Microwave-assisted α-amination of α-branched aldehydes.

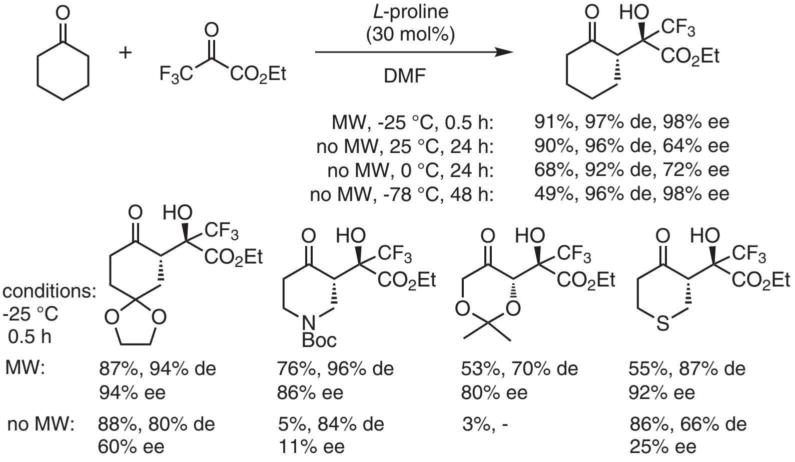
Bräse’s group [38] also developed a microwave-assisted α-sulfamidation of 2-arylaldehydes and ketones with chloramine-T catalyzed by L-proline (2 mol%). Under optimized conditions (200 W, 60 °C, 30 min, with air cooling) products were obtained in high yields (71–91%) but unfortunately no information about enantioselectivity was reported.

In 2009 Diaba and Bonjoch [39] described an interesting organocatalytic desymmetrization of a prochiral 4-*N*-protected aminocyclohexanone through its intramolecular aldolization catalyzed by a proline derivative (Scheme 21.15). The authors observed high-temperature tolerance for the enantioselectivity in this reaction (70% ee at 25 and 100 °C). The use of microwave heating (300 W, 100 °C, 15 min) resulted in better yield (70% versus 41%) and nearly unchanged enantioselectivity (65–70% ee).



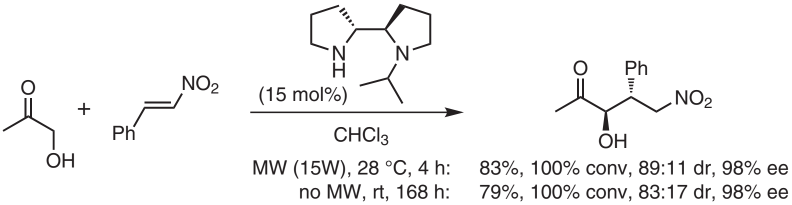
Scheme 21.15 Organocatalytic intramolecular aldol reaction.

Landge and Török [40] have applied the microwave irradiation at subzero temperatures for the enantioselective reaction of ethyl trifluoropyruvate with ketones (Scheme 21.16). In the model aldol reaction with cyclohexanone, irradiation at –25 °C reduced the reaction time to 0.5 h. A similar yield using the conventional approach was obtained at room temperature after 24 h, with markedly lower enantioselectivity. To demonstrate the scope of the method, microwave and conventional control experiments were carried out at –25 °C for 30 min using other cyclic ketones (Scheme 21.16). Surprisingly, in many cases, under microwave conditions the enantioselectivities were remarkably higher than those obtained with the classical method at the same temperature (e.g., improvements from ca. 10–20% to 90% ee). Although some experiments proved the increase of yield under MW irradiation (e.g., from 5% to 76%), there were cases where the effect was reversed. Unfortunately, this intriguing work is the only example concerning asymmetric organocatalysis under low temperature with microwave irradiation.



Scheme 21.16 Aldol reaction with microwave irradiation at subzero temperatures.

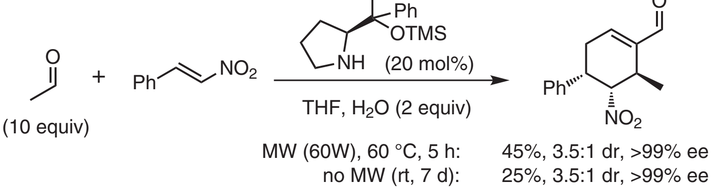
The next part of this section is focused on organocatalytic reactions with Michael-type acceptors (nitroalkenes, α,β-unsaturated aldehydes, and ketones). In 2006 Mossé and Alexakis [34] investigated the asymmetric conjugated addition of hydroxyacetone and isovaleraldehyde to β-nitrostyrene in chloroform catalyzed by *N*-isopropyl-bipyrrolidine (Scheme 21.17). Under MW heating (15 W), using simultaneous external cooling, the Michael adduct was obtained with very good yield (83%) and excellent enantioselectivity (98% ee). The results obtained without microwave irradiation were similar in terms of yield and enantioselectivity (79% and 98% ee); however, the reaction was completed after 7 days, in contrast to only 4 h under the MW conditions. Similar effects were observed in the conjugate addition of isovaleraldehyde to β-nitrostyrene and in this case the reaction time was reduced from 2 days to 1 h. The authors claimed that a specific microwave effect may be involved in the Michael addition in nonpolar solvent in contrast to, for example, the aldol reaction in polar solvent where thermal effects predominate.



Scheme 21.17 Asymmetric conjugate addition of hydroxyacetone to β-nitrostyrene.

Russo, Leadbeater, and Lattanzi [41] investigated analogous reactions of aldehydes and ketones with β-nitrostyrene catalyzed by L-proline in polar solvents (alcohols). For the model reaction of cyclohexanone and β-nitrostyrene in ethanol the results obtained using microwaves (100 W) and conventional heating were essentially identical (90% yield, 35–38% ee; with 20 mol% of L-proline at 60 °C for 2 h).

An organocatalytic microwave-assisted quadruple cascade reaction of β-nitrostyrenes with an excess of acetaldehyde in the presence of (*S*)-diphenylprolinol TMS-ether was described by Enders [42] and coworkers (Scheme 21.18).

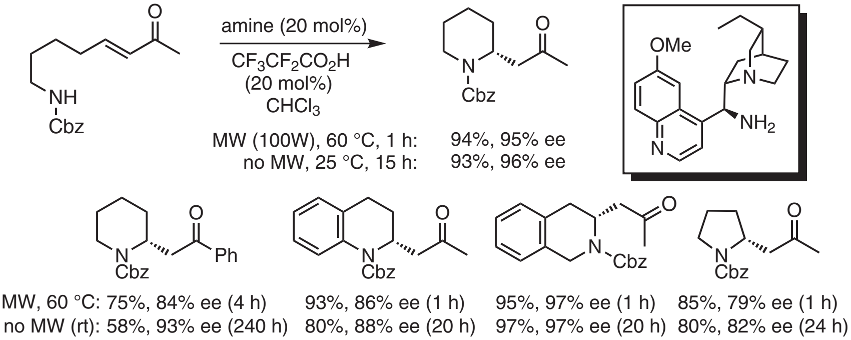


Scheme 21.18 Organocatalytic quadruple cascade reactions of acetaldehyde and β-nitrostyrene.

The formation of trisubstituted cyclohexenecarbaldehyde is a result of subsequent Michael addition, Henry condensation, Michael addition, and aldol condensation. Under classical conditions, at room temperature, the product was obtained in 25% of yield and >99% ee after 7 days. In comparison, when the reaction was performed with microwave irradiation at 60 °C for 5 h the yield increased to 45% and the ee was still very high (>99% ee). Other aromatic nitroalkenes were also tested under the MW conditions, giving 25–40% yields and high enantioselectivities (89–99% ee).

Russo's [43] group studied a microwave-assisted solvent-free addition of diethyl malonate to various enones catalyzed by L-proline. The Michael reaction was usually conducted with MW heating at 55 °C for ca. 2 h. The yields and enantioselectivities of investigated reactions strongly depend on enone structure; the best results were achieved for acyclic enones with an aryl group at the β-position. With sterically more congested enones, for example, 3-methyl-2-cyclopenten-1-one, practically racemic products with low yields were obtained.

Recently, Fustero *et al.* [44] reported an efficient microwave-assisted intermolecular aza-Michael reaction catalyzed by 9-amino-9-deoxy-*epi*-hydroquinine (20 mol%) with pentafluoropropionic acid co-catalyst (Scheme 21.19). Chiral five- and six-membered aza-heterocycles, for example, piperidines and pyrrolidines, were synthesized with high enantioselectivities. Cyclization using microwave irradiation at 60 °C allowed a reduction of reaction time (e.g., from 20 to 1 h) and led to comparable results in terms of yield and enantioselectivity to the conventional method at room temperature. Unfortunately, no comparison of microwave heating with conventional oil bath heating at 60 °C was presented.



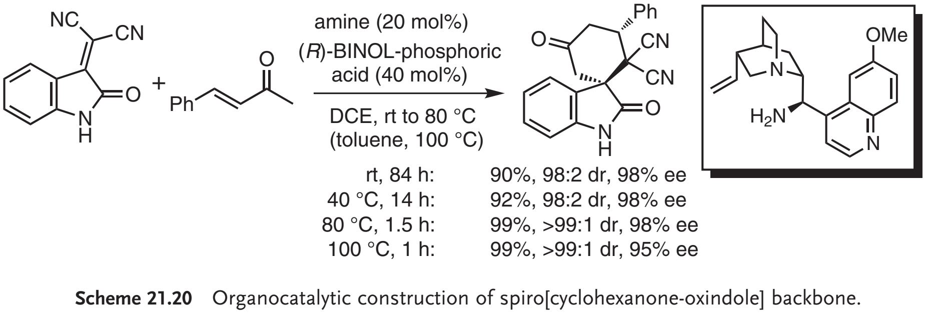
Scheme 21.19 Organocatalytic enantioselective intramolecular aza-Michael reaction.

The influence of microwave irradiation was also investigated in organocatalytic Diels–Alder and Friedel–Crafts reactions. Mossé and Alexakis [34] studied the asymmetric Diels–Alder reaction between cyclopentadiene and cinnamaldehyde catalyzed by a first-generation MacMillan imidazolidinium · HCl salt in MeOH/H_2O. Comparable results were obtained (72–82%, 78–85% ee) using microwave irradiation (50 W) and conventional oil bath heating at the same temperature and reaction time (65 °C, 1 h). However, compared to the MacMillan [45] result at room temperature the reaction is thermally accelerated with a decrease in enantioselectivity. Application of microwave irradiation in the Friedel–Crafts alkylation of *N*-methylpyrrole with crotonaldehyde catalyzed by a chiral TFA salt of aziridine carbinol led to a drop in enantioselectivity (from 60% to 36% ee); however, the yield remained on the same level [46].

Conventional heating at a relatively high temperature (>70 °C) was also successfully applied to selected organocatalytic reactions. A few examples of such highly enantioselective reactions with a high-temperature tolerance are presented below.

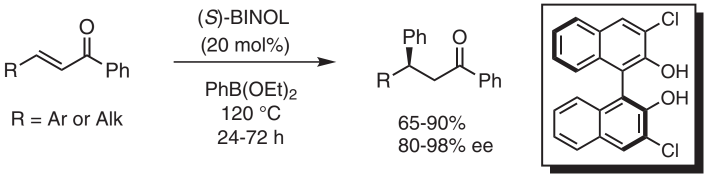
In 2005 Soós and coworkers [47] investigated an enantioselective organocatalytic conjugate addition of nitromethane to chalcone (Scheme 21.1) catalyzed by thiourea-based cinchona derivatives. This reaction was very efficient at 75 °C (94% and 90% ee). Application of a higher temperature (100 °C) was also possible, but it resulted in lower yield and enantioselectivity (68% and 85% ee) as well as catalyst decomposition. The same reaction was studied by Yang and Du [12] with thermally more stable chiral squaramides derived from cinchona alkaloids as catalyst. The product was obtained in very high yield and enantioselectivity in boiling toluene and at 130 °C in chlorobenzene (92–94%, 93% ee). When the reaction was carried out in 1,2-dichloroethane at 25 °C (62%, 90% ee after 72 h) and at 80 °C (97%, 94% ee after 48 h) even slightly better enantioselectivity was observed at higher temperature. A temperature of 70 °C was found to be optimal in several organocatalytic Friedel–Crafts alkylations of indole with enones in the presence of chiral primary amine salts [30]. An increase in temperature reduced the reaction time and produced indole derivatives with good yield and enantioselectivity (e.g., 90% and 88% ee with benzylideneacetone).

In 2011 Lan *et al.* [48] reported an efficient construction of the spiro[cyclohexanone-oxindole] backbone catalyzed by a combination of a chiral cinchona-based primary amine and (*R*)-BINOL-phosphoric acid. It was found that the reaction proceeded much faster with the elevation of temperature from room temperature to 80 °C, without affecting either the diastereoselectivities or enantioselectivities (Scheme 21.20).


NC
CN
O
N
H
+
Ph
O
amine (20 mol%)
(R)-BINOL-phosphoric
acid (40 mol%)
DCE, rt to 80 °C
(toluene, 100 °C)
Ph
O
CN
CN
O
N
H
OMe
N
H₂N
N
rt, 84 h: 90%, 98:2 dr, 98% ee
40 °C, 14 h: 92%, 98:2 dr, 98% ee
80 °C, 1.5 h: 99%, >99:1 dr, 98% ee
100 °C, 1 h: 99%, >99:1 dr, 95% ee

Scheme 21.20 Organocatalytic construction of spiro[cyclohexanone-oxindole] backbone.

Finally, Chong [49] has observed a high-temperature tolerance in asymmetric conjugate arylboration of enones catalyzed by a BINOL-derivative (20 mol%). At 120 °C the products were obtained with good yields (65–90%) and enantioselectivities (80–98% ee), both for diaryl and aryl-alkyl enones (Scheme 21.21).



Scheme 21.21 Enantioselective phenylboration of enones catalyzed by BINOL.

In conclusion, microwave irradiation can be a useful tool for accelerating asymmetric organocatalytic reactions, especially with a higher-temperature tolerance. However, for several reactions presented in this section similar or almost identical results in terms of yield and enantioselectivity were obtained with conventional heating at the same temperature. There are also examples where under microwave conditions an increase in yield and/or enantioselectivity were observed. Unfortunately, because of relatively little exploration of this area, it is still hard to speak about specific or non-thermal microwave effects. Therefore, in-depth mechanistic studies are required.

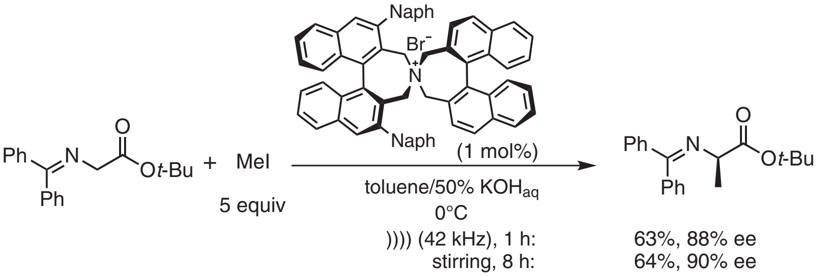
21.4
Asymmetric Organocatalysis under Ultrasound Irradiation

Ultrasonic irradiation is a very useful technique that can be utilized to increase the efficiency and reduce the time of various homogenous and heterogeneous organic reactions [50]. Ultrasound-assisted organic synthesis has been investigated with increased attention since the mid-1980s. Nowadays, sonochemistry has found many applications in organic synthesis, including polymers; however, examples of ultrasound-assisted organocatalytic reactions are still very rare in the literature [5].

This technique involves the use of high-frequency waves above 20 kHz, which generate vibrations of liquid medium and pressure changes. This leads to the formation of cavitation bubbles, which collapse in liquids and provide extreme local conditions (high pressure, rapid heating to high temperatures, and rapid cooling). Such unique conditions obtained by ultrasound irradiation can improve the efficiency of various chemical reactions [50]. Besides the cavitation phenomenon, the imploding gas-filled bubbles cause turbulent flow and mixing of liquids, which enhance diffusion and mass transfer.

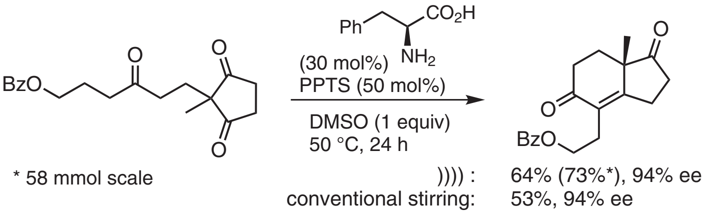
The first examples of asymmetric organocatalytic reactions accelerated by ultrasound irradiation concern the application in phase-transfer catalysis. In 1995, Mirza-Aghayan *et al.* [51] reported a heterogeneous Michael addition of *N*-acetylaminomalonate to chalcone, in the presence of a chiral phase-transfer catalyst (*N*-benzyl-*N*-methylephedrinium bromide) and potassium hydroxide. The reaction was realized in toluene as well as in the absence of the solvent. The authors observed that sonication enhances the rate of the reaction by 4–5 times with no loss of enantioselectivity compared to conventional stirring. For the reaction carried out without solvent at 60 °C for 5 min the product was isolated in 82% yield and 40% ee. This phenomenon is connected to homogenization of the reaction mixture and mass transfer enhancement.

A few years later Maruoka and coworkers [52] investigated the influence of ultrasonic irradiation on an asymmetric phase-transfer alkylation of glycinate-benzophenone Schiff base catalyzed by a chiral C_2-symmetric ammonium salt (1 mol%) in toluene and 50% KOH aqueous solution (Scheme 21.22). In this case sonication also significantly enhanced the reaction rate and reduced the reaction time from 8 to 1 h. Moreover, the enantioselectivity of the product was comparable with those obtained in the reaction with conventional stirring.



Scheme 21.22 Asymmetric phase-transfer alkylation under ultrasound irradiation.

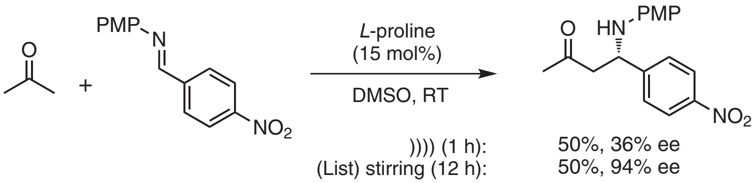
In 2005 Shigehisa *et al.* [53] applied sonication to accelerate an asymmetric intramolecular aldol condensation catalyzed by L-phenylalanine in a highly concentrated solution (Scheme 21.23). The use of this technique improved the yield from 53% to 64% and even to 73% in large scale (58 mmol), without loss of enantioselectivity (94% ee). The product presented in Scheme 21.23 was converted into



Scheme 21.23 Ultrasound-assisted intramolecular aldol condensation.

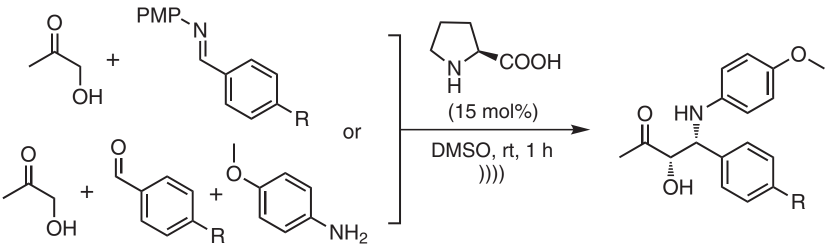
the key intermediate in the synthesis of (+)-wortmannin. This protocol was successfully applied for the synthesis of various C4-substituted tetrahydroindandiones and octahydronaphthalenediones (57–89%, 80–93% ee). Only in reactions of simple triketones (synthesis of Wieland–Miescher and Hajos–Parrish ketones) was the enantioselectivity very low.

In 2006 Kantam *et al.* [54] reported two- and three-component asymmetric Mannich reactions catalyzed by L-proline in DMSO under ultrasonic conditions. Initially, the reaction with acetone was studied, and after sonication for 1 h the Mannich product was obtained in 50% yield and surprisingly low enantioselectivity (36% ee) (Scheme 21.24). Under conventional conditions with stirring the reaction afforded the corresponding product with similar yield after 12 h and significantly higher enantioselectivity [55]. In this reaction the ultrasonic experiment shows a significant increase in reaction rate. An analogous reaction with cyclohexanone resulted in a much lower yield (15%) [54].



Scheme 21.24 Mannich reaction of acetone under ultrasonic conditions.

In this publication more attention was focused on Mannich-type reactions between imines and hydroxyacetone (Scheme 21.25). A proline catalyzed two- and three-component asymmetric Mannich reaction with hydroxyacetone was carried out for 1 h under ultrasonic conditions, affording products with excellent yields (90–98%) and enantioselectivities (85–99% ee). Only with *p*-methoxybenzaldehyde was the product obtained with lower enantioselectivity (66–81%). For the sonicated three-component Mannich reaction the results were similar to those reported by List [55b]; however, the classical method required a longer reaction time (3–24 h) and higher loading of proline (20 mol%). In a two-component Mannich reaction with electron-rich aldehydes (R = H, Me, OMe) comparative experiments without sonication were also performed [54]. The results showed that the yields after 1 h were only slightly lower; however, the sonication improved the enantioselectivity (e.g., for R = Me from 85% to 98% ee). The authors suggested that ultrasonic conditions also promote imine formation between the aromatic aldehydes and *p*-anisidine, which can explain the acceleration in the three-component reaction.



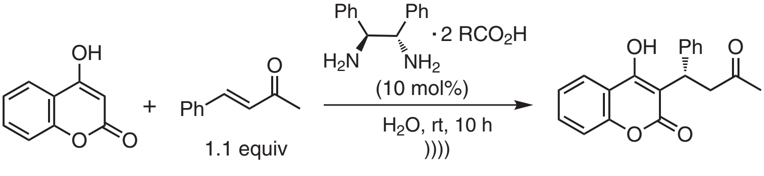
		R = NO_2	R = Br	R = H	R = Me	R = OMe
two-component	)))):	98%, 99% ee	96%, 98% ee	94%, 98% ee	90%, 98% ee	91%, 81% ee
	stirring:	---	---	93%, 93% ee	86%, 85% ee	85%, 65% ee
		(94:6 dr)	(94:6 dr)	(90:10 dr)	(85:15 dr)	(75:25 dr)
three-component	)))):	98%, 99% ee	96%, 96% ee	90%, 85% ee	---	85%, 66% ee
	stirring*:	92%, 99% ee	90%, 98% ee	83%, 93% ee	85%, 86% ee	88%, 61% ee

*List conditions: *L*-proline (20 mol %), rt, 3-24 h, DMSO. (*ref.* [55b])

Scheme 21.25 Asymmetric Mannich reaction under ultrasound conditions.

The same group also investigated a self-Mannich reaction of aliphatic aldehyde (propanal) with *p*-anisidine under ultrasonic conditions (1 h) [54]. After subsequent reduction with sodium borohydride the corresponding aminoalcohol was obtained with good yield (80%) and selectivity (95 : 5 dr, 91% ee). In this case it is difficult to evaluate the effect of ultrasound because no comparative studies under conventional conditions were reported.

Recently, Młynarski’s group [56] demonstrated an ultrasound-assisted asymmetric synthesis of warfarin via Michael addition of 4-hydroxycumarin to benzylideneacetone on water (Scheme 21.26). The reaction was effectively catalyzed by 1,2-diphenylethylenediamine with an acid co-catalyst. Importantly, the solid reactants and catalysts used were insoluble in water, and the efficiency of the reaction depends on the contact between them. Sonication enhances the dispersion process of solids on a water surface, allowing better contact between reactants. Młynarski’s



with AcOH)))) : 98%, 68% ee
with AcOH stirring (20 h): 30%, 70% ee
with $PhCO_2H$)))) : 93%, 72% ee
with $PhCO_2H$)))) : 78%, 70% ee *
* with 2 mol% of cat.

Scheme 21.26 Ultrasound-assisted synthesis of warfarin.

group shown that, compared to conventional stirring, sonication has a remarkable effect on the yield (30% versus 98%). They also emphasized that the reaction protocol allows the reaction to be scaled up (up to 2 g) without loss of enantioselectivity with only 2 mol% of catalyst. Finally, the solid product can be separated from the water phase by simple filtration, and crystallization affords optically pure warfarin.

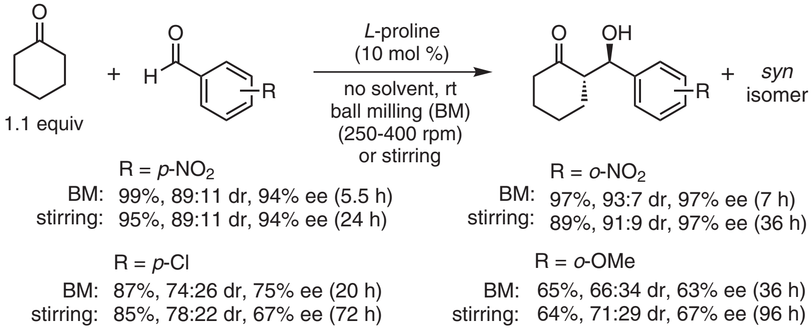
Sonochemical activation can strongly improve a wide range of chemical transformations; however, the influence of ultrasound on asymmetric organocatalytic reactions is still a very weakly explored area. Based on reported examples it could be a very attractive and useful technique for accelerating organocatalytic reactions in heterogeneous systems (e.g., phase-transfer catalysis or reaction with solid substrates on water). Evaluation of the usefulness of ultrasound in homogenous systems (e.g., in enamine activation) is still difficult and this topic requires more systematic studies in the future.

21.5
Asymmetric Organocatalysis under Ball Milling Conditions

Ball milling (BM) is a well-known methodology in material science and inorganic chemistry. Over recent years, this technique has also been more widely utilized in solvent-free organic synthesis [57], including some asymmetric organocatalytic reactions [5]. The basic principles of this technique are grinding, crumbling, and efficient mixing of solid materials. A typical ball mill is a cylindrical device filled with the grinding medium, which in most cases are balls made of inert materials. During mill rotation, collisions and friction between the balls themselves and the wall of the mill result in material grinding and mixing as well as efficient contact of the reagents. The milling also leads to a high increase in local temperature and pressure at the collision sites and a global increase of internal temperature. Some ball mills are also equipped with cooling and heating systems, which allow temperature control during the reaction. Thus, the technique is especially useful and more efficient when at least one reactant is solid and the process requires continuous fresh contact between the reacting components. Ball milling also affects chemical processes by an enhancement of reagent transport under solvent-free conditions [58].

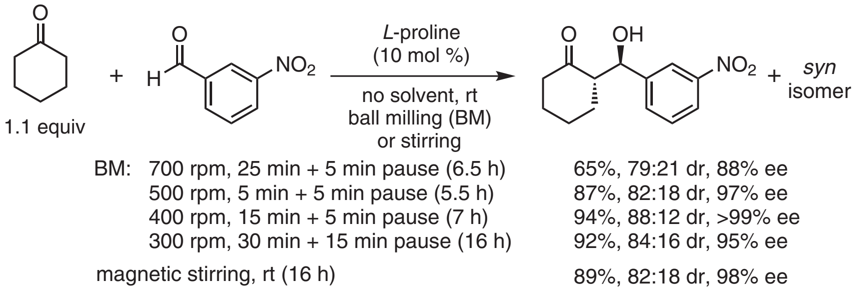
The use of ball mills to assist solvent-free asymmetric organocatalytic processes is still very rare. In 2006 Bolm and coworkers [59] reported the first examples of such applications. This technique was used in a proline catalyzed aldol reaction between ketones and aromatic aldehydes. The asymmetric organocatalytic aldol reaction was very intensively studied since the pioneering work by List and Barbas in 2000/2001 [21]. In the vast majority of cases it was performed in different organic solvents (e.g., DMSO, DMF), but in recent years several eco-friendly solvent-free, or using water, protocols have been reported. Such reactions, avoiding the use of organic solvents, are especially preferred in industrial-scale processes and the synthesis of pharmaceuticals.

Bolm [59–61] applied ball-milling to an asymmetric solvent-free aldol reaction catalyzed by L-proline (Scheme 21.27). Especially, reactions of cyclohexanone (1.1 equiv) and various crystalline aromatic aldehydes were studied under the ball-milling conditions (250–400 rpm) at room temperature. To evaluate the effect of the mechanochemical technique, comparative studies using conventional stirring were carried out for each reaction.


1.1 equiv
L-proline
(10 mol %)
no solvent, rt
ball milling (BM)
(250-400 rpm)
or stirring
+ *syn* isomer
R = *p*-NO2
BM: 99%, 89:11 dr, 94% ee (5.5 h)
stirring: 95%, 89:11 dr, 94% ee (24 h)
R = *o*-NO2
BM: 97%, 93:7 dr, 97% ee (7 h)
stirring: 89%, 91:9 dr, 97% ee (36 h)
R = *p*-Cl
BM: 87%, 74:26 dr, 75% ee (20 h)
stirring: 85%, 78:22 dr, 67% ee (72 h)
R = *o*-OMe
BM: 65%, 66:34 dr, 63% ee (36 h)
stirring: 64%, 71:29 dr, 67% ee (96 h)

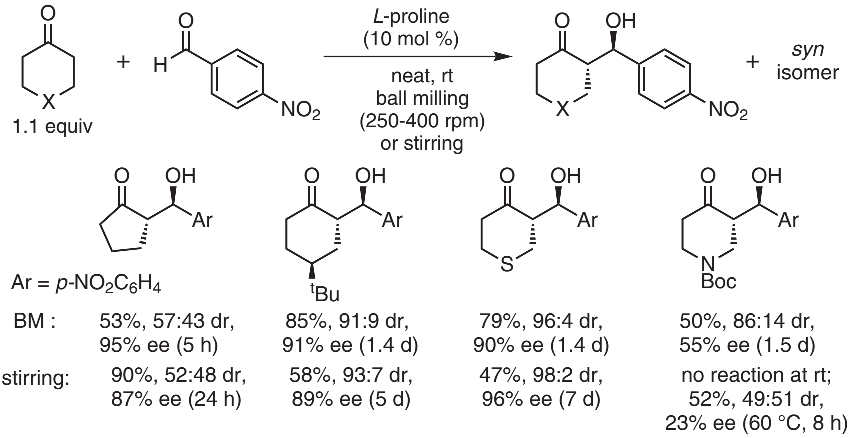
Scheme 21.27 Asymmetric organocatalytic ball-milling aldol reaction.

The authors observed that ball-milled reactions proceeded faster (usually 5–7 h instead of 16 h or more) with comparable enantioselectivity (Scheme 21.27). The best results in terms of yield and enantioselectivity were obtained with aldehydes containing electron-withdrawing groups. They then reported studies describing the influence of milling parameters on the reaction of cyclohexanone with 3-nitrobenzaldehyde (Scheme 21.28) [60]. The optimal milling conditions were found with a rotation speed of 400 rpm for 15 min followed by a 5 min pause for cooling and repeating this cycle 21 times (7 h overall time). Cooling is very important in this protocol, to avoid overheating and maintain high enantioselectivity. Decreasing or increasing the rotational speed had a negative effect on the yield and ee.


1.1 equiv
L-proline
(10 mol %)
no solvent, rt
ball milling (BM)
or stirring
+ *syn* isomer
BM: 700 rpm, 25 min + 5 min pause (6.5 h) 65%, 79:21 dr, 88% ee
500 rpm, 5 min + 5 min pause (5.5 h) 87%, 82:18 dr, 97% ee
400 rpm, 15 min + 5 min pause (7 h) 94%, 88:12 dr, >99% ee
300 rpm, 30 min + 15 min pause (16 h) 92%, 84:16 dr, 95% ee
magnetic stirring, rt (16 h) 89%, 82:18 dr, 98% ee

Scheme 21.28 Influence of milling parameters on the solvent-free aldol reaction.

Other liquid ketones such as cyclopentanone and acetone, as well as solid ketones (e.g., 4-*tert*-butylcyclohexanone, tetrahydro-4*H*-thiopyran-4-one, and 1-Boc-4-piperidone) were also examined in a proline catalyzed aldol reaction with *p*-nitrobenzaldehyde (Scheme 21.29).

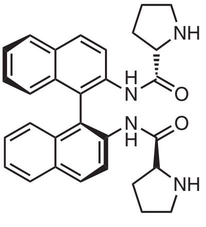

1.1 equiv
X
NO2
L-proline (10 mol %)
neat, rt
ball milling (250-400 rpm)
or stirring
syn isomer
Ar = p-NO2C6H4
tBu
S
N
Boc
BM :
53%, 57:43 dr, 95% ee (5 h)
85%, 91:9 dr, 91% ee (1.4 d)
79%, 96:4 dr, 90% ee (1.4 d)
50%, 86:14 dr, 55% ee (1.5 d)
stirring:
90%, 52:48 dr, 87% ee (24 h)
58%, 93:7 dr, 89% ee (5 d)
47%, 98:2 dr, 96% ee (7 d)
no reaction at rt; 52%, 49:51 dr, 23% ee (60 °C, 8 h)

Scheme 21.29 Scope of proline catalyzed ball-milling aldol reaction.

The reactions of solid ketones with solid aldehyde proceed much more slowly (1–1.6 days) than the reactions of liquid ketones, even though the use of solid reactants in many cases resulted in formation of a liquid phase. The reaction was also possible in ball mill when no phase change was observed (e.g., for 1-Boc-4-piperidone with *p*-nitrobenzaldehyde). In such cases the mechanochemical method was faster (1–1.6 days) compared with conventional stirring (5–7 days).

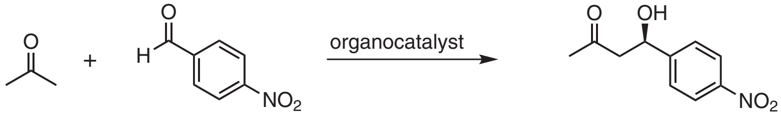
The application of ball mills in a proline-catalyzed solvent-free organocatalytic aldol reaction has several advantages: reactions proceed faster than under magnetic stirring, often with a high yield of *anti*-aldol products and very high diastereoselectivities and enantioselectivities. Reactions proceed efficiently and cleanly with almost equimolar amounts of reactants and with a catalytic amount of inexpensive proline and, in addition, isolation of the product from the reaction mixture is easier.

Another proline-based catalyst was also tested in solvent-free aldol reactions under ball-milling conditions, for example, derivatives of 1,1′-binaphthyl-2,2′-diamine or proline-based dipeptides. Nájera [62] and coworkers used a combination of (S_a)-binam-bis-L-prolinamide and benzoic acid to catalyze a direct aldol reaction under solvent-free conditions using conventional magnetic stirring. In addition, comparative studies with ball milling (400 rpm) were carried out for the reaction of cyclohexanone and 4-nitrobenzaldehyde but no improvement was observed. After 1.5 h quantitative conversion and similar diastereoselectivity and enantioselectivity were obtained using these methods [62]. Moreover, a study of the reactions of two heterocyclic ketones (tetrahydro-4*H*-thiopyran-4-one and 1-Boc-4-piperidone) found no significant differences between stirring and milling [63].



(S_a)-binam-*L*-Pro

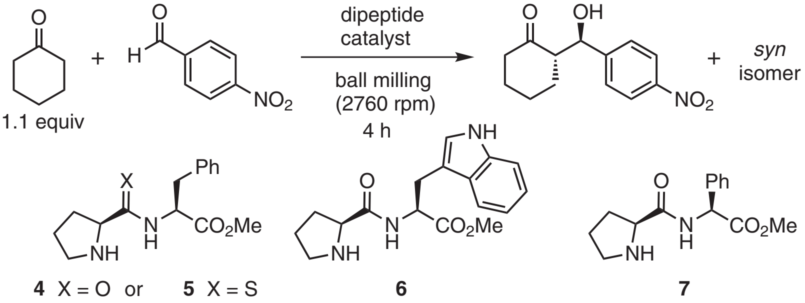
Recently, Hernández and Juaristi [64] reported an application of high-speed ball milling (HSBM; 2760 rpm) in aldol reactions of acetone, cyclohexanone, and cyclopentanone with aromatic aldehydes. L-Proline-containing dipeptides were successfully applied as catalysts. Initially, the reaction of acetone and *p*-nitrobenzaldehyde with L-proline-L-phenylalanine methyl ester (7 mol%) was studied using HSBM at −20 °C (Scheme 21.30). In a relatively short time (4 h) the aldol product was obtained with a good yield and 69% ee. This reaction with the same catalytic system under ambient conditions with stirring was investigated by Tang *et al.* [65] and after a considerably longer time resulted in good yield and low enantioselectivity (28% ee). The reaction with L-proline and milling was also less efficient (73%, 56% ee) [59].



	L-Pro-*L*-Phe-OMe		
(3 equiv)	(7 mol%)	BM (2760 rpm), -20 °C, 4 h:	82%, 69% ee
(>27 equiv)	(20 mol%)	stirring, rt, 24-48 h (*ref* [65]):	88%, 28% ee
(2 equiv)	*L*-proline (10 mol%)	BM (400 rpm), rt, 19 h: stirring, rt, 36 h:	73%, 56% ee 69%, 54% ee

Scheme 21.30 Dipeptide catalyzed ball-milled aldol reaction with acetone.

Juaristi's group focused more attention on the reactions of cyclohexanone with aromatic aldehydes. Application of HSBM in the model reaction with *p*-nitrobenzaldehyde (Scheme 21.31 and Table 21.3) and dipeptide **4** as a catalyst at room temperature led to the aldol product with high yield but low diastereo- and enantioselectivity (2 : 1 dr, 33% ee). The selectivity increased remarkably when the reaction was carried out at lower temperatures (−20 °C) and even better results were obtained with a smaller amount of catalyst (9 : 1 dr, 95% ee). It was also proved that increasing the milling frequency (from 2760 to 3080 rpm) did not influence the yield, but had a negative effect on the enantiomeric excess (75% ee at 3080 rpm versus 95% ee at 2760 rpm). In addition, the influence of additives (water, benzoic acid) and other dipeptides (**6**, **7**) on the reaction outcome was studied. The addition of water improved the efficiency of the reaction with dipeptide **6**, which contains L-tryptophan, and very encouraging results were obtained in the presence of only 1 mol% of catalyst [66]. Finally, the combination of 3 mol% of catalyst **6**, 1.1 equiv of water, and 5 mol% of benzoic acid was found to be optimal. Recently, the same group also studied the aldol reaction under ball milling conditions with analogous thiodipeptides (e.g., **5**) [67]. In some cases the proline-containing thiodipeptides proved to be better organocatalysts than their analogous amides, especially in terms of *syn/anti* selectivity (up to 98 : 2 dr).



Scheme 21.31 Model aldol reaction under high-speed ball milling conditions.

Table 21.3 Results for the model aldol reaction (Scheme 21.31).

Catalyst (mol%)	Additive (mol%)	Time (h)	Temperature (°C)	Yield (%)	*Anti/syn*	ee (%)
4 (22)	–	4	30	96	67 : 33	33
4 (22)	–	4	–20	99	80 : 20	72
4 (7)	–	4	–20	**92**	**90 : 10**	**95**
6 (7)	–	4	–20	86	86 : 14	85
7 (7)	–	4	–20	80	89 : 11	82
6 (7)	H_2O (110)	4	–20	90	91 : 9	92
6 (1)	H_2O (110)	4	–20	68	91 : 9	90
6 (3)	H_2O (110) + $PhCO_2H$ (5)	**6**	**–20**	**88**	**92 : 8**	**98**
4 (3)	H_2O (110) + $PhCO_2H$ (5)	6	–20	89	93 : 7	94
5 (7)	–	6	–20	**89**	**98 : 2**	**91**

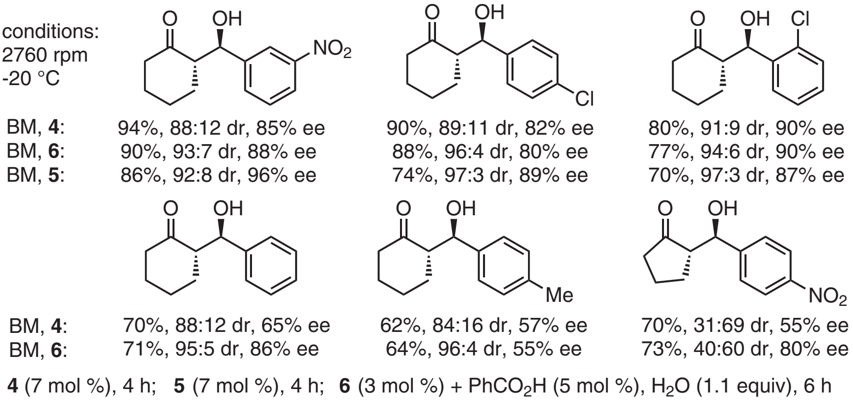
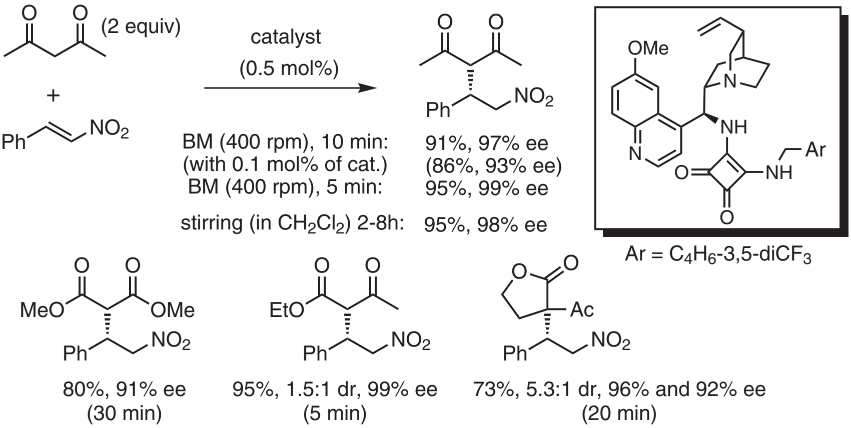


Figure 21.6 Scope of ball-mill assisted asymmetric aldol reaction catalyzed by dipeptides.

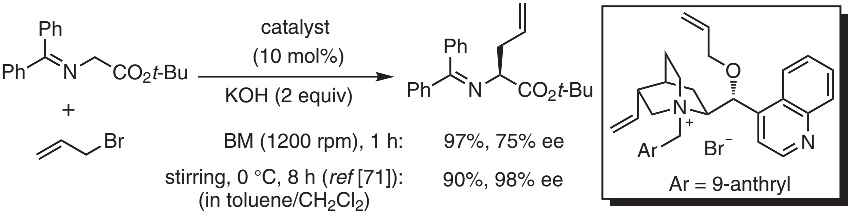
A broad range of aromatic aldehydes was tested under optimal conditions in the aldol reaction with cyclohexanone using high-speed ball milling at −20 °C with dipeptide catalysts **4–6** (Figure 21.6). The reactions of benzaldehydes substituted with electron-withdrawing groups generally lead to *anti*-aldol products in higher yields and enantioselectivities. In the solvent-free methodology dipeptides showed superior catalytic activity, both in terms of reaction time and catalyst loading as well as selectivities, compared to L-proline as organocatalyst. Unfortunately, no results of proline catalyzed aldol reaction using HSBM at −20 °C were presented. A lack of information about comparative studies using conventional stirring at −20 °C for the aldol reaction of cyclohexanone with dipeptide catalysts also makes it difficult to evaluate the high-speed ball milling technique. Based on analogous reactions under conventional conditions we assume that the effect seems to be significant. In conclusion, Juaristi’s group developed a very efficient protocol for solvent-free aldol reaction with low catalyst loading under ball-mill conditions.

In 2012 Wang *et al.* [68] reported a very fast, solvent-free organocatalytic Michael addition of 1,3-dicarbonyl compounds to nitroolefins using a planetary ball mill (Scheme 21.32). Bifunctional cinchona-based squaramides are very active and efficient organocatalyst in this reaction. Optimization of the milling process shows that even 5 min rotation is enough for completion of the model reaction (95% yield, 99% ee). The Michael addition proceeds well even with only 0.1 mol% of the catalyst within 10 min. In comparison, after conducting the reaction using classical conditions in dichloromethane as a solvent the product was obtained in very good yield and enantioselectivity after 2–8 h [69]. Various nitroolefins and 1,3-dicarbonyl compounds were tested in the ball mill assisted Michael reaction. Generally good yields (63–95%) and high enantioselectivities (91–99% ee) were obtained with 0.5 mol% of the catalyst.



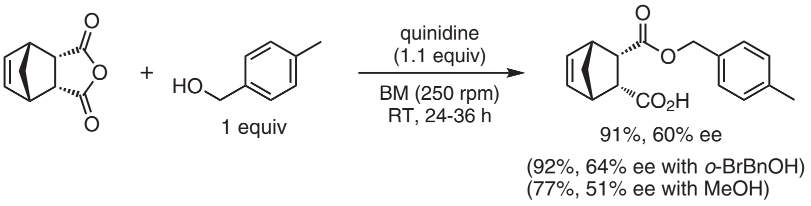
Scheme 21.32 Squaramides as an organocatalyst for asymmetric Michael additions.

Recently, Lamaty and coworkers [70] demonstrated asymmetric phase-transfer catalyzed alkylation of *tert*-butyl glycinate-benzophenone Schiff base under solvent-free ball milling conditions (Scheme 21.33). The reaction proceeds with different alkylating agents in the presence of the cinchonidine-derived ammonium salt (10 mol%) with very high yields (91–97%). This protocol reduces the reaction time; however, the enantioselectivity (36–75% ee) is lower compared to conventional method with solvents (>90% ee) [71].



Scheme 21.33 Alkylation of N-protected glycine ester under ball-milling conditions.

Ball milling was also used in alkaloid-mediated, solvent-free asymmetric opening of cyclic *meso*-anhydrides with equimolar amounts of alcohols (Scheme 21.34) [59, 72]. The reaction requires a stoichiometric amount of alkaloid and leads to optically active hemiesters in high yields and moderate enantioselectivities (up to 64%). Decreasing the rotational speed or trying to perform the reaction with stirring led to lower substrate conversions as a result of inefficient mixing. The analogous reaction at room temperature in solution usually requires an excess (3 equiv) of the alcohol to achieve high conversion of the *meso*-anhydride with comparable enantioselectivity.



Scheme 21.34 Solvent-free asymmetric opening of *meso*-anhydrides with alcohols in a ball mill.

Organocatalysis under solvent-free conditions meets very well the green chemistry requirements and has gained much attention in recent years. Ball milling is a very attractive technique that can improve the efficiency of solvent-free organocatalytic reactions and can reduce the level of organic wastes (e.g., excess of reagents). Until now, ball milling applications in asymmetric organocatalysis are still rare. This technique was successfully applied to the solvent-free organocatalytic aldol reaction and conjugate addition of 1,3-dicarbonyl compounds to nitroolefins.

21.6
Summary and Conclusions

Nowadays asymmetric organocatalysis is a very powerful and useful tool in the synthesis of chiral molecules and can be an interesting alternative to selected metal-catalyzed reactions. Despite the many advantages of this methodology, a large group of organocatalytic reactions is slow and requires high catalyst loadings or is still not accessible using classical approaches. These drawbacks can be solved partly through the use of non-classical techniques, for example, high-pressure, microwave heating, ultrasound irradiation, and ball milling. In this chapter we have analyzed only enantioselective versions of organocatalytic reactions.

The first example of an asymmetric reaction catalyzed by chiral organic molecules assisted by a non-classical technique was a high-pressure Michael reaction reported by Matsumoto in 1981. Until 2004, studies on non-classical activation in asymmetric organocatalysis were practically limited to the use of high pressure. In most of the investigated reactions high pressure has a positive effect on the yield but, unfortunately, usually the enantioselectivity decreases. The most promising results were obtained by Hayashi for the Mannich reaction under 2 kbar at –20 °C. In this case, pressure strongly accelerates the reaction rate while retaining high enantioselectivity. Recently, a significant effect of hydrostatic pressure on the difficult organocatalytic 1,4-conjugate additions to prochiral sterically congested β,β-disubstituted enones with high enantioselectivity was also demonstrated. In our opinion the high-pressure technique is a very promising method that can be successfully used to increase the efficiency of various difficult asymmetric organocatalytic reactions characterized by a negative volume of activation.

Since 2005/6, increasing interest was observed in the application of other non-classical techniques in organocatalysis, which resulted in ca. 30 publications where the effect of non-classical "activation" was discussed. Especially, the influence of microwave heating and solvent-free ball milling was examined. Sonication is still not very well explored in this context and its applicability was mostly proved for heterogeneous systems. The microwave technique provides more effective energy transfer to the reaction mixture and several groups reported that it can positively influence organocatalytic reactions utilizing iminium and enamine catalysis. In some reactions higher enantioselectivity was also observed with microwave irradiation. However, in this case it is difficult to generalize the advantages of this technique because in some reactions there was no evidence for specific or non-thermal microwave effects and similar results were achieved using conventional heating methods. Finally, ball milling is a very valuable technique that can improve the efficiency of solvent-free organocatalytic reactions. We hope that this chapter will help the reader to better and reliably evaluate the advantages of non-classical methods in organocatalysis and stimulate further investigation into this topic in the future.

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22
Ionic Liquid Organocatalysts

Dmitry E. Siyutkin, Alexander S. Kucherenko, and Sergei G. Zlotin

22.1
Introduction

Modern organocatalysts, in particular bi- and polyfunctional organocatalysts bearing chiral amine, peptide, alkaloid, thiourea, and some other units, are rather expensive. Major difficulties associated with homogeneous catalysts are the separation and purification of organic products and recovery of precious chiral catalysts from the reaction mixture at the end of the process. Many strategies have been proposed to overcome these challenges, including changes in the reaction medium and modifications of the catalyst structure. Desirable reaction media should be nontoxic and environmentally safe, ensure an efficient removal from product, and be reusable. In the past decade, ionic liquids (ILs) [1], supercritical CO_2 [2], fluorous systems [3, 4], and water [5–7] have emerged as promising candidates. Among them, ILs, which are simply a low-melting composition of ions, drew considerable attention as green reaction media for various chemical reactions [1], including catalytic transformations [8–10], in particular those in the presence of chiral catalysts [11–13]. The increasing interest in ILs is explained by their favorable physical (low vapor pressure, high thermal, and chemical stability) and solvent properties (high polarity and ability to dissolve a wide range of organic molecules [14]). Most ILs are available materials that do not evaporate and are easy to contain. Their exceptional solubility characteristics make them good candidates for multiphasic catalysis. For example, their solubility in water depends on the nature of the anions, temperature, and the length of the alkyl chains on the cation. An advantage of using ILs as polar media in organocatalytic reactions is their ability to dissolve an organocatalyst and sustain it in the IL-phase during a catalytic transformation and working-up procedure, providing simple isolation of product and catalyst recovery. Furthermore, ionic liquids bearing chiral structural fragments (CILs, chiral ionic liquids) sometimes appear useful as stereocontrolling media for chiral recognition and asymmetric synthesis [15, 16].

ILs also show great promise as recyclable supports for homogeneous catalysts [17–19], in particular chiral ones [16, 20–23]. Once introduced into a catalyst structure, ionic groups (IL fragments) significantly reduce (but not to zero) the

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solubility of a catalyst in organic and/or aqueous phases and remarkably facilitate recovery of the catalyst and purification of products. Ionic-liquid supports offer a better loading capacity than solid (polymeric or inorganic) supports. Furthermore, there emerges the opportunity of tuning the physicochemical properties of a catalyst and its performance in organocatalytic transformations by varying the cation and/or anion nature and analyzing it by conventional NMR or MS techniques.

Recent advances and opportunities that ILs and their congeners offer as solvents for, or as an integral part of, organocatalysts are reviewed in this chapter.

22.2
Ionic Liquids as Recyclable Solvents for Asymmetric Organocatalytic Reactions

In recent years a lot of information related to the use of ionic liquids as media for organocatalytic reactions catalyzed by chiral amine derivatives has been reported [11, 13, 24]. ILs specifically solvate polar enamine or iminium intermediates generated from a carbonyl substrate and a catalyst and significantly polarize nucleophilic or electrophilic compounds that enantioselectively interact with these intermediates (Figure 22.1), leading to a rise in reaction rates, sometimes at the expense of a slight drop in the enantiomeric enrichment of products as compared with similar reactions in organic solvents [12].

22.2.1
α-Amino Acid-Promoted Reactions in IL Media

The IL medium is most beneficially applied for asymmetric reactions promoted by hydrophilic amino acid organocatalysts, in particular proline. Amino acids, being poorly soluble in hydrocarbon or ether solvents, are not "washed out" to the organic phase during products isolation, which allows the catalyst–IL system

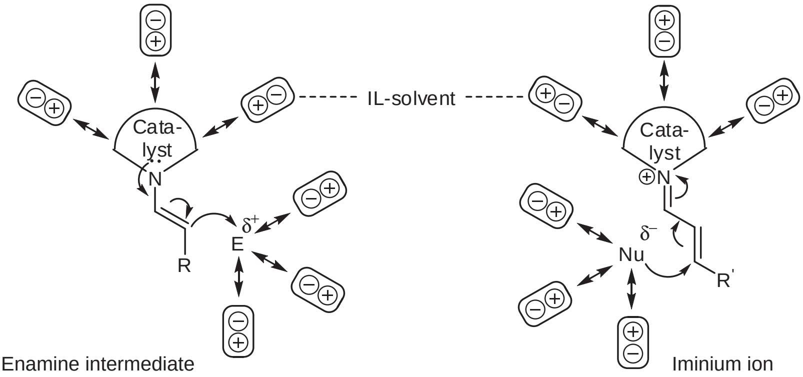
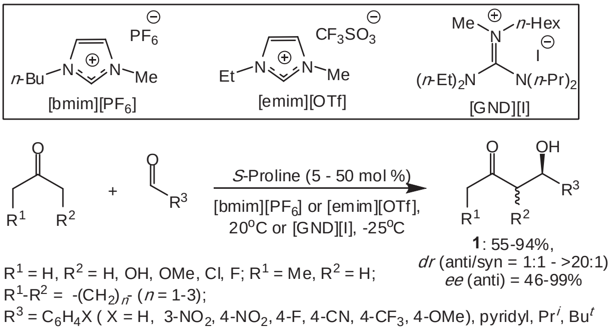


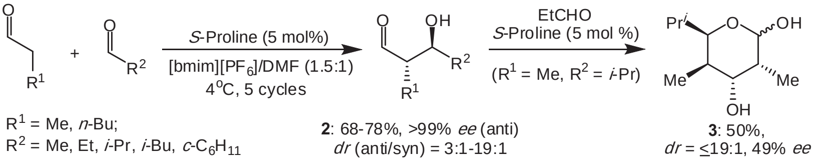
Figure 22.1 Specific solvation of enamine or iminium intermediates and polar reagents in the IL-media.

recovery. Asymmetric aldol reactions are among the most popular organocatalytic transformations in IL media. In 2002, Toma [25] and Loh with coworkers [26] independently found that (*S*)-proline-catalyzed reactions of acetone or cycloalkanones with aromatic aldehydes could be carried out in molten 1,3-dialkylimidazolium salt/ketone mixtures to give aldols **1** in moderate to high yields and an enantiomeric excess comparable to that obtained in DMSO (Scheme 22.1). Later, this methodology was extended to acetone derivatives bearing a heteroatom at the α-position to the carbonyl group [27] and to heteroaromatic aldehydes [28]. Aldol reactions with cycloalkanone donors predominantly afford *anti*-aldols and water and/or another IL additive (up to 10 equiv.) may exert beneficial effect on reaction diastereoselectivity [29]. The IL nature plays an important role here: the yield and enantiomeric excess of aldols **1** ($R^1 = R^2 = H$) increased (up to 99%) when the reactions ran in hexa- or pentaalkylguanidinium salts, for example, [GND][I] [30]. 4-Phenoxy-(*S*)-proline-catalyzed reactions of acetone with benzaldehyde derivatives in a acetone/[bmim]PF_6 (1 : 1) mixture afforded chiral aldols not contaminated with crotonization by-products [31].


PF6
n-Bu
Me
[bmim][PF6]
CF3SO3
Et
Me
[emim][OTf]
Me
n-Hex
I
(n-Et)2N
N(n-Pr)2
[GND][I]
R1
R2
R3
S-Proline (5 - 50 mol %)
[bmim][PF6] or [emim][OTf], 20°C or [GND][I], -25°C
OH
1: 55-94%,
dr (anti/syn = 1:1 - >20:1)
ee (anti) = 46-99%
R1 = H, R2 = H, OH, OMe, Cl, F; R1 = Me, R2 = H;
R1-R2 = -(CH2)n- (n = 1-3);
R3 = C6H4X (X = H, 3-NO2, 4-NO2, 4-F, 4-CN, 4-CF3, 4-OMe), pyridyl, Pri, But

Scheme 22.1 (*S*)-Proline-catalyzed cross-aldol reactions of alkanones with aldehydes in an IL medium.

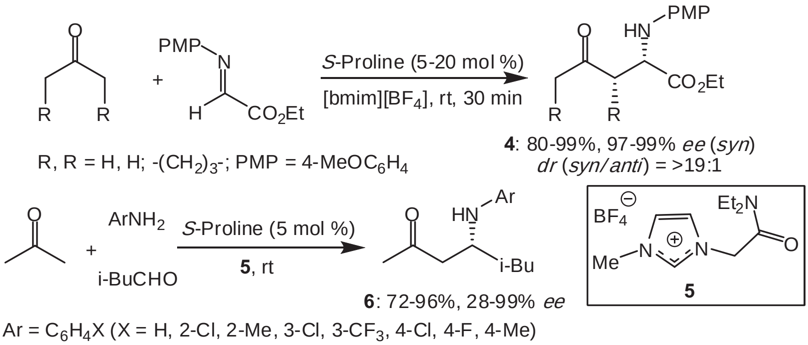
Córdova discovered that proline-catalyzed cross-aldol reactions between two aliphatic aldehydes were markedly accelerated and had exceptionally high enantioselectivity (up to 99% ee) in IL/DMF mixtures (Scheme 22.2) [32]. Notably, the required catalyst loading was significantly lower (1–5 mol%) in this case than in



Scheme 22.2 (*S*)-Proline-catalyzed cross-aldol reactions between aliphatic aldehydes in the [bmim][PF_6]/DMF solvent system.

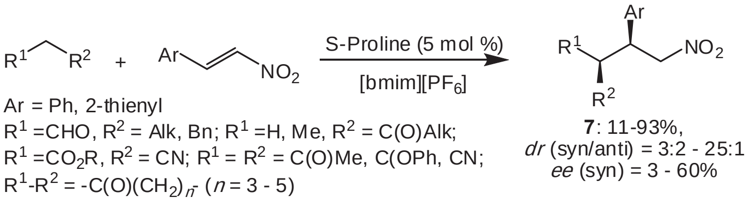
organic solvents. Under the proposed conditions, generated aldols **2** reacted with the third aldehyde molecule to give hydroxypyran derivatives, for example, compound **3.** The proline/IL/DMF system was regenerated and used five times without affecting either yield or selectivity.

Proline-catalyzed two- or three-component Mannich reactions proceed efficiently in IL media. Barbas III with coworkers performed proline-catalyzed reactions of N-PMP-protected ethyl α-iminoacetate with acetone or cyclohexanone in [bmim][BF_4] and obtained chiral adducts **4** with the predominant *syn*-configuration in high yields and enantioselectivities (Scheme 22.3) [33]. A more than fourfold increase in the process rate was attained in the IL medium compared with the same reactions in organic solvents. However, an attempt to extend this methodology to hydroxyacetone as a nucleophile failed: while the desired amino alcohol product was obtained with excellent yield, the reaction diastereo- (*syn*/*anti* 68 : 32) and enantioselectivity (3–24% ee) was much worse than in organic solvents. Xu and coworkers found that the proline-catalyzed asymmetric Mannich reaction of aniline derivatives with acetone and isovaleric aldehyde could be carried out as a one-pot process in IL **5** functionalized with the amide group to afford Mannich adducts **6** in high yield [34]. However, when methyl ketones rather than acetone were selected as starting materials, the targeted Mannich products were hard to obtain. Another limitation was poor enantioselectivity (28–33% ee) in reactions involving *ortho*-substituted arylamines.



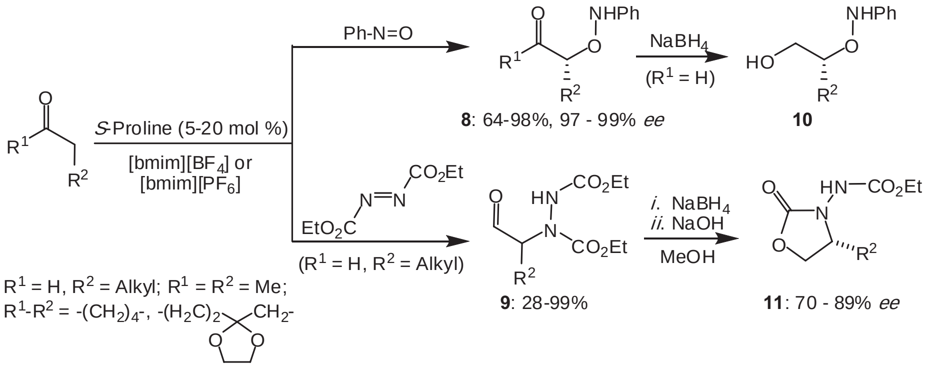
Scheme 22.3 (*S*)-Proline-catalyzed two- and three-component Mannich reactions in ILs.

Organocatalytic asymmetric Michael reactions were first performed in IL media by Toma and coworkers [35]. Carbonyl or 1,3-dicarbonyl compounds reacted with β-nitrostyrene or 2-(β-nitrovinyl)thiophene in [bmim][PF_6] in the presence of proline to afford corresponding Michael adducts **7** in moderate to high yields and in some cases with rather high *syn*-diastereoselectivities (Scheme 22.4). The enantioselectivity of the processes, however, was poor (≤60% ee). 1,3-Diketones appeared less active donors than ketones and especially than aldehydes in the IL medium.


S-Proline (5 mol %)
[bmim][PF6]
Ar = Ph, 2-thienyl
R1 =CHO, R2 = Alk, Bn; R1 =H, Me, R2 = C(O)Alk;
R1 =CO2R, R2 = CN; R1 = R2 = C(O)Me, C(OPh, CN;
R1-R2 = -C(O)(CH2)n- (n = 3 - 5)
7: 11-93%,
dr (syn/anti) = 3:2 - 25:1
ee (syn) = 3 - 60%

Scheme 22.4 (*S*)-Proline-catalyzed asymmetric Michael reactions in an IL medium.

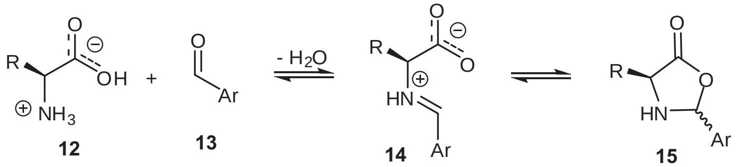
Aldehydes and ketones could be asymmetrically α-amino-oxylated [36, 37] or α-aminated [38] to corresponding poly-functional compounds **8** and **9** by proline-catalyzed reactions with nitrosobenzene or diethyl azodicarboxylate in molten imidazolium salts (Scheme 22.5). As compared to those in common solvents, the yields of α-aminoxylation products **8** of both aldehydes and ketones improved significantly in the IL medium and the enantioselectivity was excellent. Yields and enantiomeric enrichment of hydrazino-aldehydes **9** were somewhat lower. The ionic environment considerably accelerated the processes and the (*S*)-proline/IL system could be quantitatively recovered after completion of the aminoxylation reaction and reused (5–6 times) without any loss of catalytic performance. Aldehyde-derived products **8** and **9** (R^1 = H) could be reduced to chiral 1,2-diol derivatives **10** or configurationally stable heterocycles **11**, which are valuable intermediates in asymmetric synthesis.



Scheme 22.5 (*S*)-Proline-catalyzed asymmetric heterofunctionalization of carbonyl compounds in an IL medium.

Organocatalytic reactions in IL media can be induced by primary α-amino acids. In 2008, Lombardo with coworkers showed that aromatic aldehydes could react with cyclic ketones in 1-butyl-1-methylpyrrolidinium trifluoromethane sulfonate ([bmpyr][OTf]) containing the catalytic system arginine/*p*-toluenesulfonic acid (10 mol% each) to give the corresponding aldols in higher yields than in DMSO

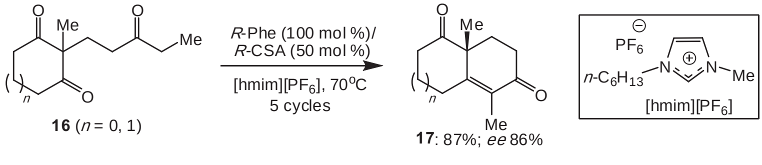
[39]. The catalytic system could be recovered; however, the conversion decreased by 10% in the second run and halved after the third catalyst recovery along with a 20% enantioselectivity drop. The authors explained the progressive catalyst deactivation by an off-catalytic cycle reaction between the α-amino acid **12** and the acceptor aldehyde **13**, resulting in the formation of the iminium ion **14** (Scheme 22.6). Subsequent cyclization of **14** to oxazolidinone **15** may impair the enantiomeric purity of the arginine catalyst and decrease the ee of aldol product. This undesirable process proceeds slowly at ambient temperature both in organic solvents and in the molten salts; however, in the long run (when the same amino acid–IL catalytic system is used several times) it starts to exert a negative impact on enantioselectivity.



Scheme 22.6 A plausible scheme for the deactivation of amino acid catalysts in an IL media.

In the same year, Teo and Chua reported that L-serine *tert*-butyldiphenylsilyl ether efficiently catalyzed an asymmetric aldol reaction between cycloalkanones and aromatic aldehydes in [bmim][BF_4] [40]. The catalyst solution in the IL withstood three recovery cycles; however, a progressive decrease of activity caused by the leaching of the siloxy serine catalyst from the IL medium to the ether solution used for extraction of products and a slight decline of reaction enantioselectivity were recorded.

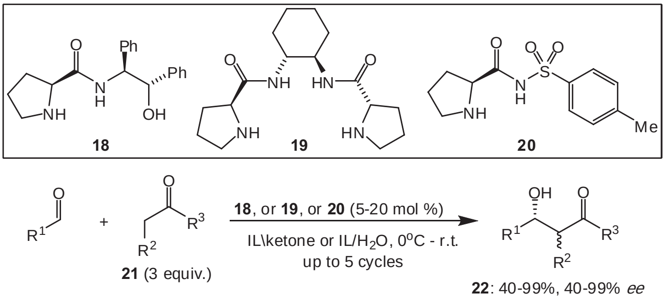
Molten imidazolium salts appeared to be suitable reaction media for α-amino acid promoted intramolecular aldol reactions. In 2007, Hagiwara with co-authors synthesized Wieland–Miescher ketone analogues **17** from triketones **16** in [hmim][PF_6] solution (hmim = 1-hexyl-3-methylimidazolium) in the presence of the (*R*)-phenylalanine ((*R*)-Phe)/(*R*)-camphorsulfonic acid ((*R*)-CSA) catalytic system (Scheme 22.7) [41]. Annulation product **17** was obtained under the proposed conditions in a high yield and with reasonably high enantioselectivity. A drawback of the developed procedure is a high catalyst loading (100 mol%). This disadvantage could be partly compensated by its recovery, though with a slight conversion reduction and a significant (20–30%) drop in enantioselectivity in the third or fourth cycle.



Scheme 22.7 Synthesis of Wieland–Miescher ketone analogues **17** in an IL medium.

22.2.2
Reactions in the Presence of Other Chiral Organocatalysts in IL Media

Prolinamide derivatives were found to be highly compatible with IL media. Asymmetric aldol reactions catalyzed by proline amide **18** [42], bis-amide **19** [43], or sulfonylated amide **20** [44] could be efficiently carried out in molten salts [bmim][BF_4] or [bmim][PF_6] (Scheme 22.8). Bis-amide **19**-catalyzed aldol reactions performed in [bmim][BF_4] required a much lower excess of donor ketone **21** (3 equiv. instead of 30 equiv. in proline-catalyzed reactions) and allowed a synthesis of chiral compounds **22** bearing heterocyclic, prenyl, or metallocene units [43]. The improved catalytic performance of prolinamide derivatives in ionic liquids might be due to a stabilization of the iminium intermediate formed from the ketone and the catalyst or because of the enhanced nucleophilicity of the enamine [42]. Notably, IL dilution with water (1 : 1 by volume) accelerated the enamine/iminium ion hydrolysis and raised reaction rates and product yields, with the enantioselectivity being retained or even becoming somewhat higher than under water-free conditions [45]. Furthermore, the catalyst/IL/water system could be easily recycled five times without aldol yield, dr, and ee losses.

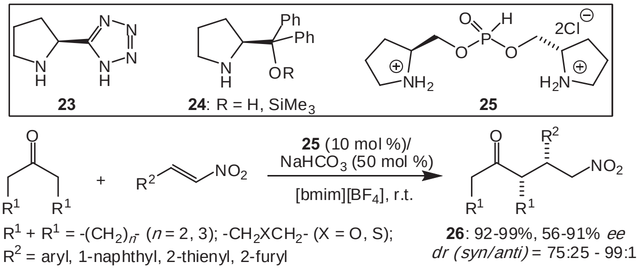

18
19
20
18, or 19, or 20 (5-20 mol %)
IL\ketone or IL/H2O, 0°C - r.t.
up to 5 cycles
21 (3 equiv.)
22: 40-99%, 40-99% ee

IL = [bmim][BF_4]; R^1 = aryl, 5-NO_2-thienyl, 2-pyridyl, 4-ferrocenyl, *n*-CpMn$(CO)_3$, alkyl
R^2 = H, OH; R^3 = Me, Et, *cyclo*-Pr, -$(CH_2)_2CH{=}C(Me)_2$; $R_2 + R_3$ = -$(CH_2)_n$- (n = 3, 4)

Scheme 22.8 Prolinamide-catalyzed asymmetric aldol reactions in an IL medium.

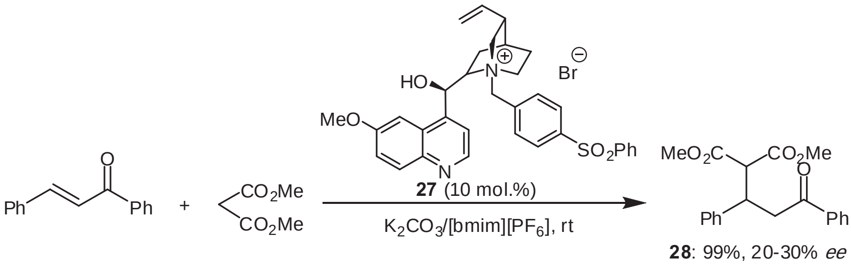
Sulfonylated prolinamide **20** [46], (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole **23**, and α,α-diphenylprolinol derivatives **24** [47] were studied by Toma with co-authors as organocatalysts of asymmetric Michael additions of carbonyl compounds to α-nitroalkenes in various ILs containing 1,3-dialkylimidazolium or 1,1-dialkylpyrrolidinium cations and fluorinated or fluorine-free anions. However, the ee values of generated Michael adducts (20–50%) were inferior to those obtained in proline-catalyzed reactions. In some cases, the sign of the products optical rotation could be changed by varying the IL anion, which was indicative of an IL effect on the transition state [47]. Promising results were attained by Wang with coworkers in asymmetric Michael reactions of cyclic ketones with β-nitrostyrene derivatives catalyzed by the dihydrochloride of bis(pyrrolidinylmethyl)phosphite **25**

(10 mol%), which was easily prepared from *N*-Boc-(*S*)-prolinol [48]. Reactions carried out in the [bmim][BF_4] medium in the presence of inorganic base ($NaHCO_3$–50 mol%) afforded corresponding Michael adducts **26** in high yields and, as a rule, with excellent *syn*-diastereoselectivity (Scheme 22.9). However, acetone gave with β-nitrostyrene product **26** (R^1 = H, R^2 = Ph), which was almost racemic (9% ee) under the proposed conditions.


23
24: R = H, SiMe3
25
2Cl⊖
25 (10 mol %)/
NaHCO3 (50 mol %)
[bmim][BF4], r.t.
R1 + R1 = -(CH2)n- (n = 2, 3); -CH2XCH2- (X = O, S);
R2 = aryl, 1-naphthyl, 2-thienyl, 2-furyl
26: 92-99%, 56-91% ee
dr (syn/anti) = 75:25 - 99:1

Scheme 22.9 IL-mediated asymmetric nitro-Michael reactions in the presence of pyrrolidine–phosphite **25.**

There is an example of alkaloid-induced asymmetric reactions in an IL medium. Dimethyl malonate reacted with chalcone under the action of potassium carbonate in the presence of quininium-derived phase transfer catalyst (PTC) **27** in a [bmim][PF_6] melt to give adduct **28** in high yield but with a slightly lower enantioselectivity than in conventional organic solvents (DMSO or toluene) (Scheme 22.10) [49]. Most surprisingly, the absolute configuration of product **28** reversed in the IL medium. Additional experiments with quinine or *N*-(4-nitrobenzyl)quininium bromide as PTC indicated that the reversal of enantioselectivity was not due to the PTC but can be attributed to the cation associated with the anion of the ionic liquid. The process was successfully repeated in the presence of the recovered IL/PTC system without a reduction in reaction rate or product yield.



Scheme 22.10 Chiral phase-transfer catalysis of the asymmetric Michael reaction in an IL medium.

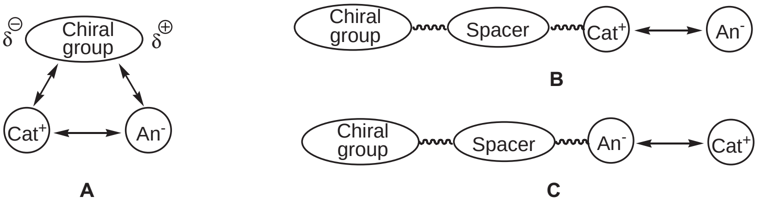


Figure 22.2 Attaching the chiral group to the ionic fragment via electrostatic interaction (A) or covalent bonding (B, C).

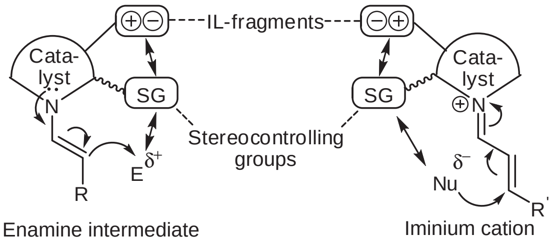


Figure 22.3 Enamine and iminium intermediates generated by IL-tagged organocatalysts.

22.3
“Non-Solvent” Applications of Ionic Liquids and Their Congeners in Asymmetric Organocatalysis

Impressive results were attained by using ionic liquids and their congeners as recyclable supports for asymmetric organocatalysts. This mode of immobilization significantly reduces catalyst solubility in the reaction medium and markedly facilitates recovery using just a catalytic amount of the ionic support [16, 20, 50–52]. Over recent years, original approaches to the preparation of immobilized organocatalysts have been developed such as those based on attaching a catalyst to an ionic fragment through the electrostatic interaction (A) [53] or tagging it to either the cation or the anion by means of a covalently bonded spacer group (B, C) (double-headed arrows designate the electrostatic interactions) (Figure 22.2) [20, 23].

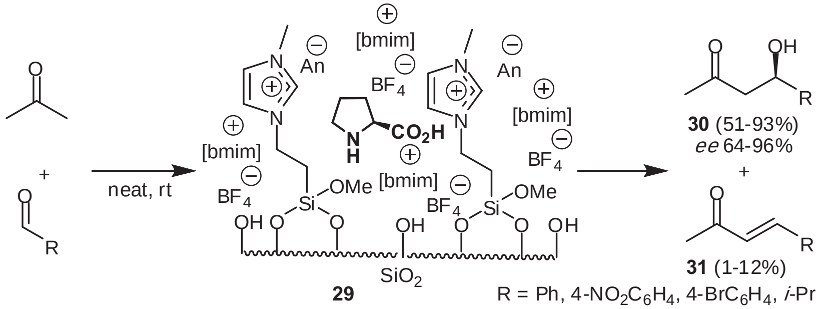
Recoverable organocatalysts of types A and especially B or C proved useful in various asymmetric reactions such as aldol, Michael and Mannich, cycloaddition, alkylation, and some other reactions. Most IL-tagged catalysts contain a secondary or a primary amino group adjacent to the stereocenter and activate carbonyl compounds through the formation of chiral enamines or iminium cations with them. These intermediates in the transition state stereoselectively interact with an electrophile or a nucleophile, respectively (Figure 22.3). In addition, there are communications on a few IL-supported catalysts that activate reagents and implement stereoinduction by asymmetric protonation, hydrogen bonding, or ion pairing [54–56]. In some cases, the ionic moiety in the catalysts plays more than a supporting role in the reaction. By varying cation or anion structures, it is possible to influence the electronic, spatial, and physicochemical properties of a catalyst, thus maximizing its activity and selectivity in a particular reaction [21–23, 57].

22.3.1

Immobilization of Organocatalysts through Electrostatic Interaction with Ionic Fragments

22.3.1.1 Biphasic Non-Covalent Immobilization on Ionic Liquids and Ionic Polymers

An efficient non-covalent approach to organocatalyst recovery is based on the ability of ionic liquid monolayers supported on a silica or polymer matrix to act as the catalyst's immobilization phase [58]. This approach allows a significant reduction of the required amount of a rather expensive ionic liquid and makes handling of the "heterogenized" catalyst more convenient. In 2004, Gruttadauria and coworkers covalently attached organic cations (imidazolium, pyridinium, or DABCO derivatives) in combination with various anions to the surface of silica gel by means of Si–O bonds (Scheme 22.11) [59, 60]. Then, more ionic liquid, for example, [bmim]BF_4, and proline were co-deposited on this monolayer to afford immobilized organocatalyst **29**, in which the ionic layer acted as a reaction medium and enabled easy recovery of the catalysts upon filtration. In the presence of this catalyst, aldehydes generate aldols **30** with acetone in reasonably good yields with satisfactory ee values. The catalyst could be reused up to six times; however, after the third recovery, the reaction enantioselectivity usually decreased. In addition, enones **31** commonly emerged as by-products.



Scheme 22.11 Asymmetric aldol reaction in the presence of proline immobilized in the ionic layer covering a modified silica-gel surface.

This methodology was applicable to silica-supported organocatalysts **32** that incorporated other types of linkers that bound imidazolium cations to the silica surface along with peptide chiral inductors (Figure 22.4). The latter gave higher enantioselectivities in asymmetric aldol reactions than corresponding catalytic systems containing proline [61].

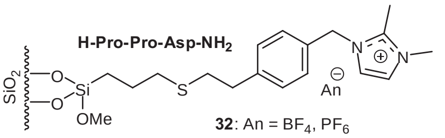
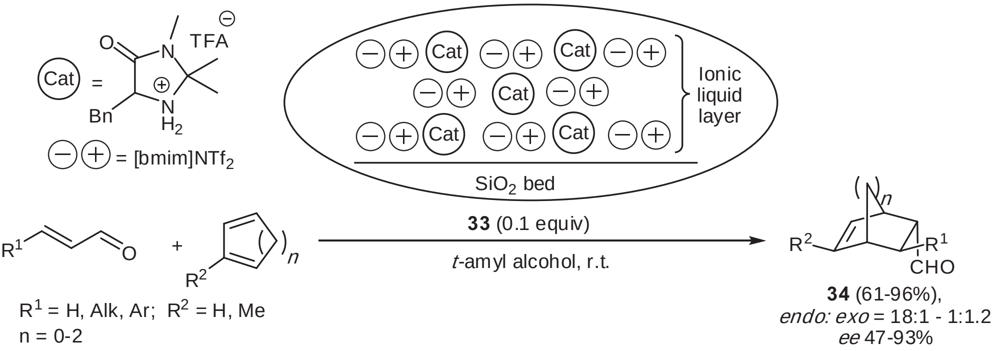


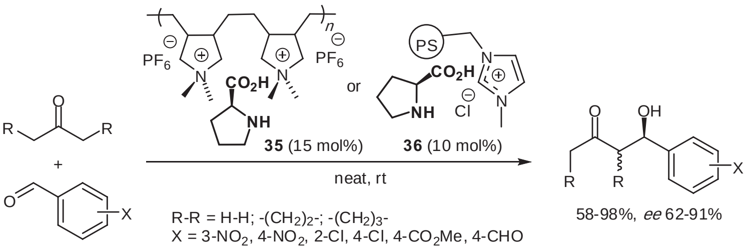
Figure 22.4 IL-supported tripeptide H-Pro-Pro-Asp-NH_2 organocatalyst.

Recently, Hagiwara and coworkers non-covalently immobilized the MacMillan imidazolidinone trifluoroacetate organocatalyst in the pores of silica gel using the ionic liquid [bmim]NTf_2 and successfully applied prepared heterogeneous catalyst **33** to an enantioselective Diels–Alder reaction (Scheme 22.12) [62] where the ionic modification of the SiO_2 surface with covalently tagged cations was not needed. The heterogeneous catalyst promoted the synthesis of various highly functionalized cycloadducts **34**, in particular unstable ones. Furthermore, it could be re-used after simple filtration up to six times.



Scheme 22.12 Enantioselective Diels–Alder cycloaddition catalyzed by the MacMillan imidazolidinone located in a supported ionic liquid phase.

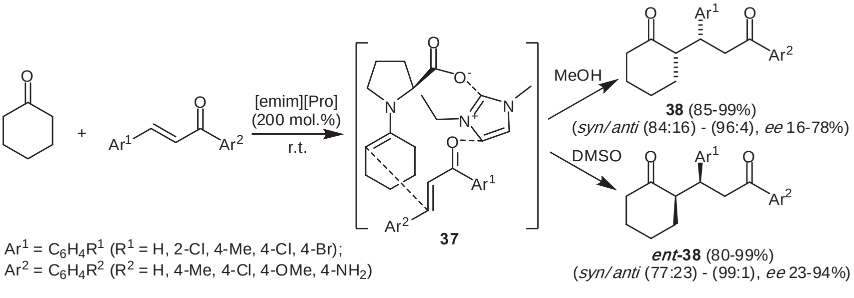
Another efficient immobilization system (**35**) [63] was prepared by immobilization of proline on the surface of solid polyelectrolyte bearing pyrrolidinium cations and PF_6^- anions typical for ionic liquids. In the presence of heterogeneous catalyst **35** (15 mol%), aldol reactions between aldehydes and ketones proceeded in good yields and with moderate to high enantioselectivity (62%–91% ee, Scheme 22.13). Proline was not washed out of the ionic support to the organic phase and, hence, catalyst **35** could be used six times without a decrease in product yields and ee. Similar results were obtained using system **36**, in which L-proline was placed on polystyrene (PS) modified with ionic groups [64]; however, polyelectrolyte system **35** was less expensive than Merrifield resin-derived catalyst **36** and contained more ionic groups, which efficiently retained amino acid on the polymer surface.


PF6
PF6
CO2H
NH
or
PS
CO2H
NH
Cl
35 (15 mol%)
36 (10 mol%)
neat, rt
R-R = H-H; -(CH2)2-; -(CH2)3-
X = 3-NO2, 4-NO2, 2-Cl, 4-Cl, 4-CO2Me, 4-CHO
58-98%, ee 62-91%

Scheme 22.13 Proline/polyelectrolyte and proline/modified polystyrene ionic systems and their use as organocatalysts in asymmetric aldol reactions.

22.3.1.2 **Ion-Pair Immobilization on Ionic Liquids**

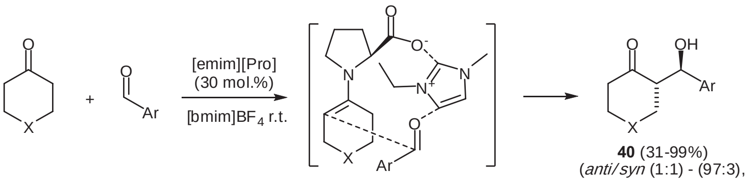
Given their dual acid–base character, α-amino acid-derived catalysts can be easily transformed into ion pairs by treatment with corresponding organic bases or inorganic acids. These ion pairs exhibit the same or even higher catalytic activity and stereoselectivity than the original α-amino acids. In 2008, Wang and coworkers discovered that anionic-type IL 1-ethyl-3-methylimidazolium prolinate ([emim][Pro]) prepared by Ohno's procedure [65] efficiently catalyzed the Michael addition of cyclohexanone to chalcones (Scheme 22.14) to give Michael adducts **38** in high yields and with moderate to high diastereo- and enantioselectivities [66]. Presumably, both starting compounds are activated by a catalyst: cyclohexanone – through the enamine formation and α,β-enone – by hydrogen bonding in transient state **37**. Surprisingly, the absolute configuration of adducts **38** depended on the solvent used, with adducts **38** produced in methanol and their enantiomers *ent*-**38** in DMSO.


[emim][Pro]
(200 mol.%)
r.t.
Ar1
Ar2
37
MeOH
DMSO
38 (85-99%)
(syn/anti (84:16) - (96:4), ee 16-78%)
ent-38 (80-99%)
(syn/anti (77:23) - (99:1), ee 23-94%)
Ar1 = C6H4R1 (R1 = H, 2-Cl, 4-Me, 4-Cl, 4-Br);
Ar2 = C6H4R2 (R2 = H, 4-Me, 4-Cl, 4-OMe, 4-NH2)

Scheme 22.14 IL [Emim][Pro]-catalyzed Michael reactions of cyclohexanone with chalcones.

Later, these researchers applied [emim][Pro] as a green and efficient asymmetric organocatalyst for direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes [67]. Where the reactions were performed in IL [bmim]BF_4 and a 30 mol% catalyst loading was used, the corresponding aldol adducts **40** were obtained in up to 99% yield with moderate to high diastereoselectivity (*anti* : *syn* up to 97 : 3) and with good to excellent ee values (up to 99%). Surprisingly, the enantioselectivity became much worse (6–9% ee) in IL [bmim]PF_6 having the

PF_6-anion. The authors attributed the difference to the stronger ionicity of the BF_4 anion as compared with the PF_6 anion and a better ability of the former to stabilize enamine transition state **39** (Scheme 22.15). After completion of the reaction and subsequent product extraction with diethyl ether, the system [emim][Pro]/[bmim] BF_4 could be reused directly in subsequent reactions (three recycles) with just a slight drop in activity and reaction stereoselectivity.



X = $-(CH_2)_n-$ (n = 0 - 2), O, S, CH(Me)

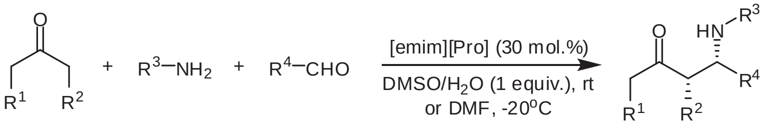
39

Ar = C_6H_4R (R = H, 2-NO_2, 2-Cl, 4-NO_2, 4-Cl, 4-F, 4-Br, 4-CF_3, 4-Me, 4-OMe, 2-furyl, 2-thienyl, 2-pyridyl

40 (31-99%)
(*anti/syn* (1:1) - (97:3),
ee 28-99%)

Scheme 22.15 [Emim][Pro]-catalyzed asymmetric aldol reactions between cycloalkanones and aromatic aldehydes.

The ion pair [emim][Pro] efficiently catalyzed multicomponent reactions of carbonyl compounds. In the presence of this catalyst a three-component Mannich reaction of ketones with aniline derivatives and aromatic aldehydes in moist DMSO or DMF was highly regio-, stereo-, and enantioselective to give *syn*-coupling products **41** (Scheme 22.16) [68]. The proposed conditions, which imply the use of dipolar aprotic solvents, did not, however, allow post-reaction IL recovery.

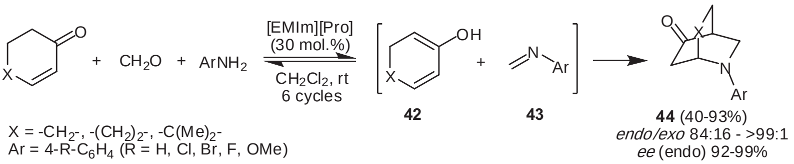


R^1 = H, Me; R^2 = H, Me, OH
R^3 = Ph, 4-$MeOC_6H_4$
R^4 = 4-R-C_6H_4 (R = H, NO_2, CN, Cl, F, Br, Me)

41 (48-99%)
syn/anti 54:46 - >99:1
ee (syn) 90 - >99%

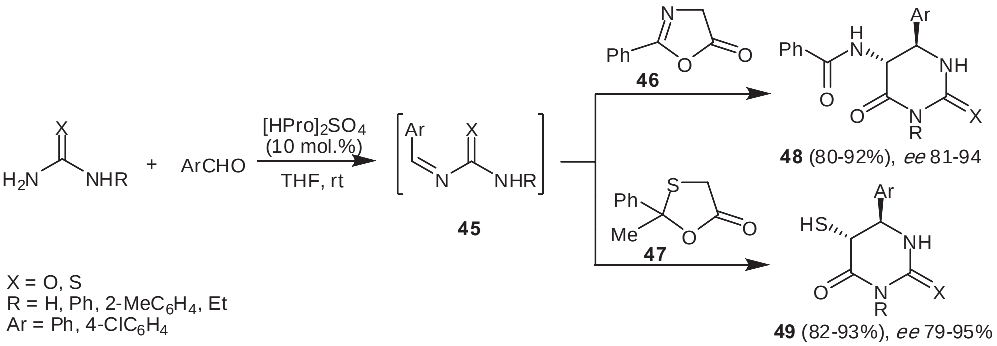
Scheme 22.16 [Emim][Pro]-catalyzed three-component Mannich reactions.

IL [emim][Pro] induced a one-pot aza-Diels–Alder reaction between cyclic α,β-unsaturated ketones, formaldehyde, and aniline derivatives [69]. Bicyclic ketones **44** having high diastereomeric and enantiomeric purity were readily produced from *in situ* generated dienols **42** and methylene-imines **43** under the proposed conditions (Scheme 22.17). The catalyst was recovered and reused in the same reaction six times, although the enantioselectivity decreased somewhat.



Scheme 22.17 [Emim][Pro]-catalyzed one-pot aza-Diels–Alder reactions.

Yadav and coworkers discovered that the available acidic IL prolinium sulfate ($[HPro]_2SO_4$) exhibited good catalytic performance in the asymmetric version of the three-component Biginelli reaction, in which 2-phenyl-1,3-oxazol-5-one (**46**) or 2-methyl-2-phenyl-1,3-oxathiolan-5-one (**47**) served as an active methylene component [70]. The reaction afforded corresponding hexahydropyrimidine derivatives **48** and **49** as single diastereomers in high yields and with moderate to high ee values (Scheme 22.18). A reaction scheme was proposed that consists of the generation of coupling products **45** from aldehydes and urea (or thiourea) derivatives and their Mannich-type reaction with carbon acid **46** or **47** followed by heterocyclization.



Scheme 22.18 $[HPro]_2SO_4$-catalyzed three-component Biginelli reactions.

22.3.2
Modification of Organocatalysts by Ionic Groups through Covalent Bonding

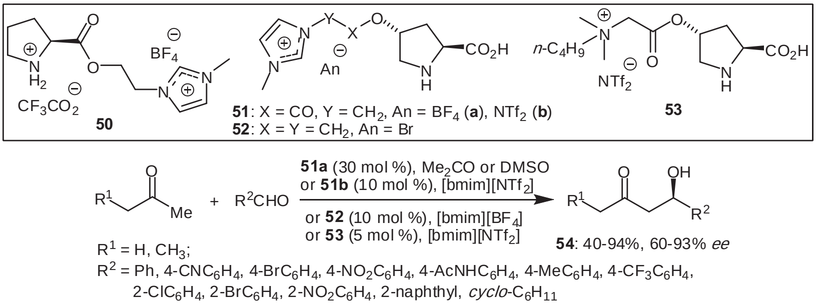
Immobilized organocatalysts of B and **C** types (Figure 22.2), in which the chiral inductor is covalently attached to the ionic group, usually exhibit better sustainability than non-covalently supported type A catalysts due to the high energy of covalent bonds. One ionic group, normally a cation, is covalently bound to the catalyst, while the exchangeable counterion allows control of the catalyst's solubility profile. The ionic moiety in these catalysts acts as a highly tunable support. Furthermore, in some cases it efficiently polarizes or stabilizes the enamine or iminium intermediates and, as a result, enhances the reaction rate.

22.3.2.1 **Ionic Organocatalysts Incorporating α-Amino Acid Units**

In recent years, α-amino acid (especially proline) derivatives incorporating ionic groups have been synthesized and gained widespread applications as recoverable organocatalysts in asymmetric aldol reactions. The catalysts commonly melt below 100–150 °C and can be considered as task-specific CILs [71].

22.3.2.1.1 **Proline-Derived Organocatalysts**

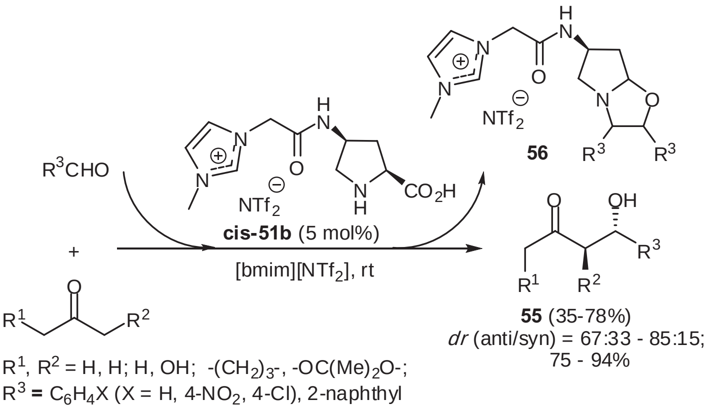
In 2006, Miao and Chan suggested two approaches to the preparation of proline-containing CILs through attachment of the catalyst carboxy or hydroxyl group to the cation unit by means of an ester spacer [72]. Synthesized compounds **50–53** exhibited different catalytic properties in the aldol reaction (Scheme 22.19). Whereas in the presence of proline ester **50** the yield of aldol **54** (R^1 = H, R^2 = 4-NCC_6H_4) did not exceed 10% at 11% ee, in the case of 4-hydroxyproline-derived catalyst **51a** the yield was 59% and the ee 72%. The results highlight an important role of the auxiliary carboxy group in asymmetric catalysis and has been taken into account in further studies on the synthesis of immobilized versions of proline-derived organocatalysts.



BF4
CF3CO2
50
An
CO2H
n-C4H9
NTf2
CO2H
51: X = CO, Y = CH2, An = BF4 (a), NTf2 (b)
52: X = Y = CH2, An = Br
53
R1
Me
+ R2CHO
51a (30 mol %), Me2CO or DMSO
or 51b (10 mol %), [bmim][NTf2]
or 52 (10 mol %), [bmim][BF4]
or 53 (5 mol %), [bmim][NTf2]
R1
OH
R2
54: 40-94%, 60-93% ee
R1 = H, CH3;
R2 = Ph, 4-CNC6H4, 4-BrC6H4, 4-NO2C6H4, 4-AcNHC6H4, 4-MeC6H4, 4-CF3C6H4, 2-ClC6H4, 2-BrC6H4, 2-NO2C6H4, 2-naphthyl, cyclo-C6H11

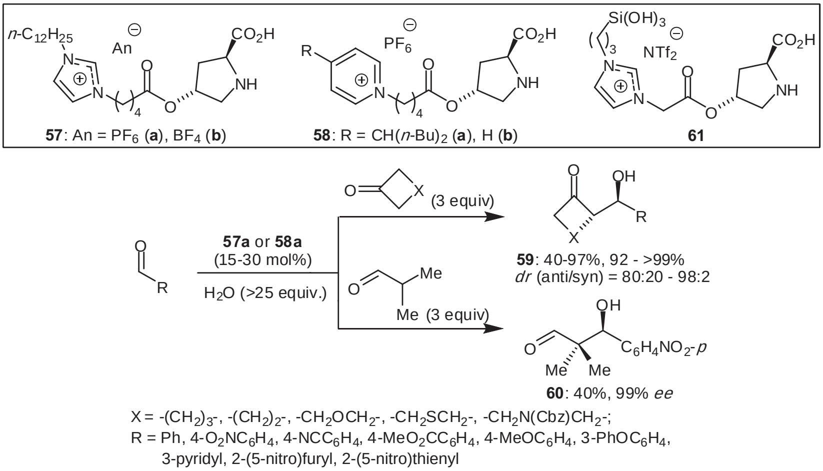
Scheme 22.19 Proline-derived CILs and their use in asymmetric aldol reactions.

In 2007, Zhou and Wang [73] and Lombardo with Trombini [74] independently replaced traditional organic solvents with ionic liquids to facilitate recovery of CIL-catalysts. Asymmetric aldol reactions between acetone and aromatic aldehydes catalyzed by proline derivative **52** afforded aldols **54** (R^1 = H) in the [bmim][BF_4] solution with yields and ee values comparable to those obtained in organic solvents. The **52**/[bmim][BF_4] system was recovered and reused six times with retained reaction enantioselectivity [73]. The load of Lombardo’s 4-hydroxyproline-derived CILs **51b** and **53** bearing bis(triflyl)imide anions in the aldol reaction between aldehydes and ketones in [bmim][NTf_2] could be reduced to 5 mol%. The results clearly indicated that the cross-aldol condensation enjoyed a significant rate acceleration using the onium-tagged proline/IL system. Furthermore, an enantioselectivity increase was recorded that corresponded to a 10–20% improvement with respect to the use of proline in DMSO or [bmim][PF_6] [25, 26]. The high affinity of ion pairs **51b** and **53** for ILs hypothesized by the authors resulted in a more organized association of the catalyst to the IL within structured domains of the solvent [75]. However, the **53**/bmim[NTf_2] system lost activity after recovery due to partial "washing away" of the catalyst to the organic phase during the aldol product extraction and/or catalyst transformation into the off-cycle oxazolidine by-product as a result of its side reaction with the aldehyde component [74]. The latter suggestion was supported by the fact that the turnover number characterizing the productivity of the isomeric catalyst *cis*-**51b** [76] in the reaction of cyclohexanone with 4-nitrobenzaldehyde increased from 17 to 380 where the reaction ran in the presence of a minor (1–2 equiv.) amount of water, which suppressed the generation of undesirable side-product **56** (Scheme 22.20) [77]. The authors [76] demonstrated the synthetic potency of catalyst *cis*-**51b** by the preparation of aldol products **55** of moderate to high enantiomeric purity from aromatic aldehydes and linear or cyclic ketones.


R³CHO
+
R¹
R²
cis-51b (5 mol%)
[bmim][NTf₂], rt
NTf₂
CO₂H
56
R³
R³
OH
R¹
R²
R³
55 (35-78%)
dr (anti/syn) = 67:33 - 85:15;
75 - 94%
R¹, R² = H, H; H, OH; -(CH₂)₃-, -OC(Me)₂O-;
R³ = C₆H₄X (X = H, 4-NO₂, 4-Cl), 2-naphthyl

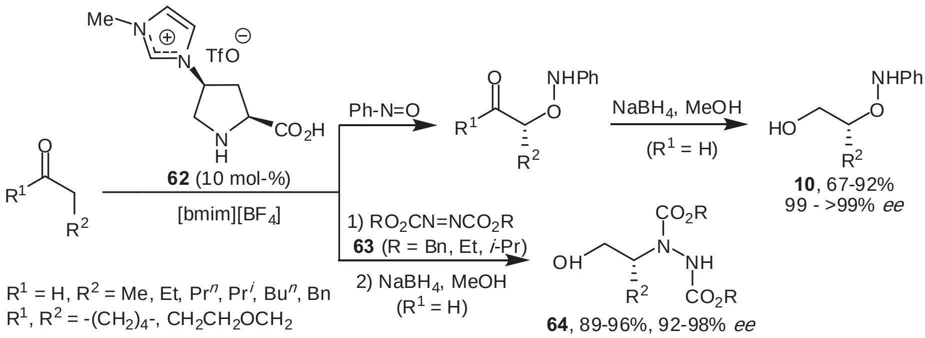
Scheme 22.20 Formation of off-cycle side-product **56** responsible for reducing the efficiency of proline-derived catalysts in the asymmetric aldol reaction.

A small amount of water was shown to exert a favorable effect on various asymmetric organocatalytic reactions in organic solvents [5, 6]. However, most hydrophilic amino acid derived organocatalysts become less active in the aqueous medium, where they exist as zwitterions unable to generate the enamine intermediates needed to trigger the catalytic cycle. We proposed an efficient method for adapting amino acid-sourced chiral IL to the aqueous medium by introducing long-chain alkyl groups and hydrophobic anions into their molecules and by performing reactions in reagents/water two-phase systems. Indeed, alkylimidazolium- and alkylpyridinium-tagged hydrophobic proline derivatives **57a** [78] and **58a** [79] (15–30 mol%) efficiently promote aldol reactions in a large water excess (25 equiv.). Under the proposed conditions aromatic or heteroaromatic [80] aldehydes reacted with cyclic ketones or branched aliphatic aldehydes in an amount of just 3 equiv. with respect to an aldehyde-acceptor to give corresponding aldol products **59** or **60** in high yields and with extremely high *anti*-diastereo- (dr up to 98 : 2) and enantioselectivities (ee up to 99%) (Scheme 22.21). Surprisingly, similar water-soluble compounds **57b** and **58b** without long-chain alkyl groups or a hydrophobic anion did not catalyze the aldol reaction in water, whereas in the presence of imidazolium salts **51b** (Scheme 22.19) or **61** bearing just a lipophilic bis(triflyl) amide anion (developed by Italian researchers [81] and [82]) a tenfold excess of donor ketone had to be used for the reaction to take place. Obviously, catalysts **51**, **57a**, **58a**, and **61** that incorporate lipophilic alkyl groups and/or fluorinated anions, along with the hydrophilic heterocyclic moiety, under the proposed conditions are located in the water/organic (reagents) phase interfacial area where the catalytic process occurs. The catalysts were easily recovered and retained their catalytic properties in 5–8 reaction cycles.


n-C12H25
An
CO2H
NH
4
57: An = PF6 (a), BF4 (b)
PF6
R
CO2H
NH
58: R = CH(n-Bu)2 (a), H (b)
Si(OH)3
3
NTf2
CO2H
NH
61
X
(3 equiv)
57a or 58a
(15-30 mol%)
H2O (>25 equiv.)
R
Me
Me (3 equiv)
OH
R
59: 40-97%, 92 - >99%
dr (anti/syn) = 80:20 - 98:2
OH
C6H4NO2-p
Me Me
60: 40%, 99% ee
X = -(CH2)3-, -(CH2)2-, -CH2OCH2-, -CH2SCH2-, -CH2N(Cbz)CH2-;
R = Ph, 4-O2NC6H4, 4-NCC6H4, 4-MeO2CC6H4, 4-MeOC6H4, 3-PhOC6H4, 3-pyridyl, 2-(5-nitro)furyl, 2-(5-nitro)thienyl

Scheme 22.21 Asymmetric aldol reactions “on water” in the presence of hydrophobic IL-tagged proline-derivatives.

Later, numerous attempts were made to increase the efficiency, operation period, and scope of IL-modified proline-containing catalyst applications by changing the location and/or the structure of the IL-tag. In 2010, Cheng and Zhu with coworkers synthesized IL **62**, containing directly linked proline and imidazolium fragments, and applied it as a supported organocatalyst for the asymmetric α-aminoxylation of aldehydes or ketones with nitrosobenzene [83] and for α-amination of aldehydes with azodicarboxylates **63** [84] (Scheme 22.22). In both cases, the best results were attained in the commercially available IL [bmim][BF_4]. The raw reaction products bearing the aldehyde group were treated without isolation by sodium borohydride to afford corresponding hydroxyl derivatives **10** or **64** in high yield and with excellent enantioselectivity. After separation of reagents and products, the catalytic system **62**/[bmim][BF$_4$] could be reused for up to seven times and the products could be obtained without a significant decrease in enantioselectivities and yields (for the L-proline-catalyzed synthesis of compounds **10** in [bmim][BF$_4$], see Section 22.2 [36, 37]).



Scheme 22.22 CIL **62**-catalyzed asymmetric α-aminoxylation and α-amination reactions of carbonyl compounds.

In 2009, Liebscher and coworkers synthesized, by click chemistry, CILs **65–67**, in which the proline fragment was attached to the 1,2,3-triazolium cation either directly or through an ether or ester spacer [85] (Figure 22.5) and applied them as recyclable organocatalysts in direct asymmetric aldol and Michael reactions under neat conditions or in the IL medium. The catalysts performed better than (*S*)-proline itself, that is, a synergistic effect of the proline unit and the IL-tag was produced. The absolute configuration of the remote stereocenter C4 of the proline unit [(*S*)- in compound **65** and (*R*)- in **66** and **67**] exerted negligible impact on the stereochemical outcome of the reactions; however, catalyst **65** appeared more robust as it retained activity over five cycles with a slightly decreased enantioselectivity.

Recently, the same authors discovered that CIL **65** could serve as an efficient promoter in asymmetric α-aminoxylation of carbonyl compounds with nitrosobenzene in IL media [86]. They managed to recycle and reuse the catalytic system **65**/[bmim]BF$_4$ up to five times; however, the enantioselectivities and yields of products **68** decreased with each recycle and the reaction time had to be increased to achieve complete conversion of the starting material. The authors explained the

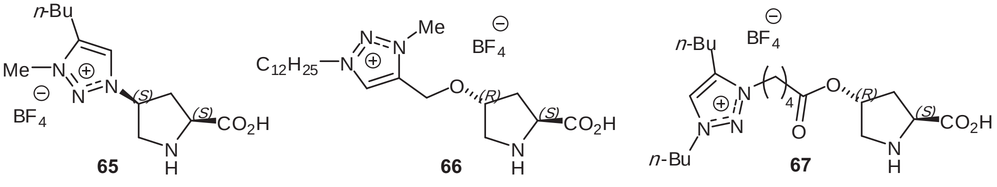
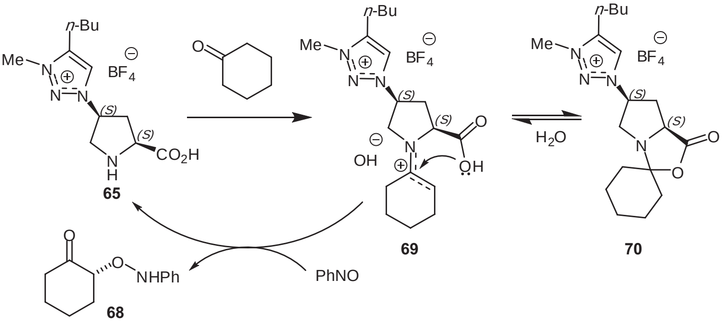


Figure 22.5 Proline derivatives tagged to 1,2,3-triazolium units.

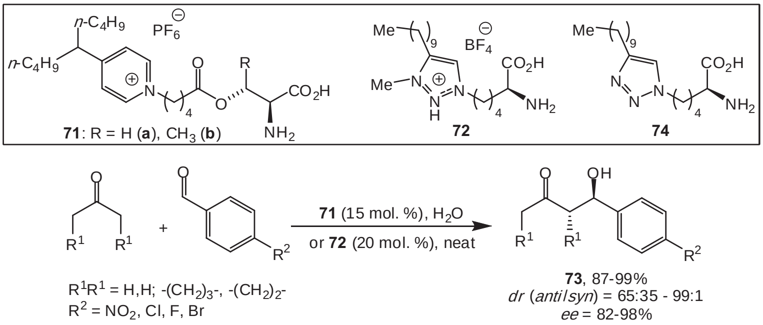
deterioration by the reversible formation of hemiacetal **70** from key iminium ion/enamine intermediate **69** (Scheme 22.23) and suggested a way to improve the recycling procedure by adding a small water amount after each recycle to accelerate hydrolysis of the off-cycle by-product.



Scheme 22.23 Formation of off-side oxazolidinone **70** in CIL **65**-catalyzed asymmetric α-aminoxylation of cyclohexanone.

22.3.2.1.2 **Primary Amino Acid-Derived Organocatalysts**

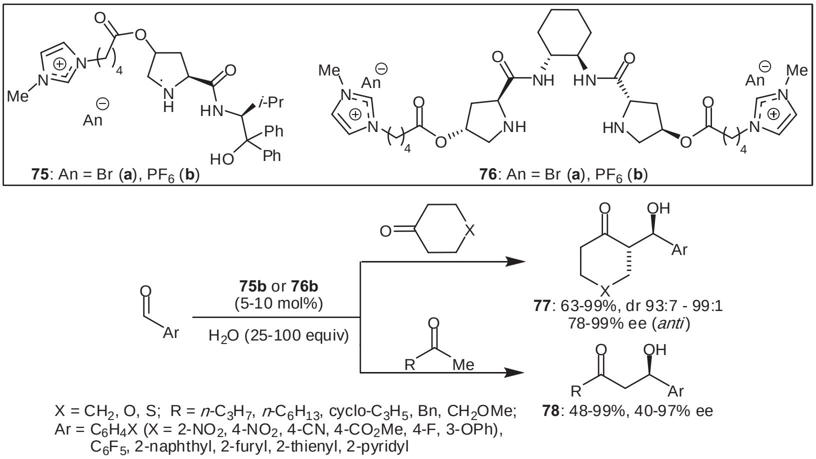
Primary amino acids, being an integral part of peptides, play a crucial role in Nature and sometimes exhibit useful organocatalytic properties [87]. In 2009, we reported the synthesis of IL-supported organocatalysts **71a** and **71b** bearing fragments of primary α-amino acid, in particular serine or threonine. These lipophilic chiral ILs appeared able to catalyze asymmetric aldol reactions in an aqueous medium. However, the activity of catalysts **71a** and **71b** as well as the diastereo- and enantioselectivity of the reactions in the aqueous environment were somewhat lower than in the presence of proline derivatives **57a** and **58a** (Scheme 22.21) [79]. In 2010, Liebscher and coworkers prepared lysine-derived compound **72**, in which the amino acid fragment was tagged to the 1,2,3-triazolium cation, and studied it as an organocatalyst in stereoselective direct aldol reactions between ketones and aromatic aldehydes under neat conditions (Scheme 22.24) [88]. In this case, 1,2,3-triazolium tetrafluoroborate **72**, bearing a primary amino acid unit, performed better in reagent media than organocatalysts with (*S*)-proline moieties and afforded aldols **73** in high yields and with reasonable stereoselectivity. Remarkably, in the presence of similar compound **74**, which contained the uncharged 1,2,3-triazol moiety instead of the 1,2,3-triazolium cation unit, the reaction of 4-nitrobenzaldehyde with cyclohexanone under the same conditions gave aldol product **73** (R^1, R^1 = $-(CH_2)_3-$, R^2 = NO_2) with the considerably lower enantioselectivity of 52% ee, versus 98% in the case of CIL **72.** This demonstrated that the triazolium tag contributed to improving the catalytic performance of **72.** Recycling and reuse of **72** was achieved by product extraction with diethyl ether; however, the catalyst activity and reaction diastereo- and enantioselectivity became somewhat lower with each cycle (total of five runs).



Scheme 22.24 Asymmetric aldol reactions catalyzed by IL-tagged serine, threonine, or lysine derivatives.

22.3.2.2 **Ionic Organocatalysts Incorporating α-Amino Amide Units**

Amino acid amides normally possess higher catalytic activity in the asymmetric aldol reactions than corresponding amino acids [89]. We synthesized IL-supported bifunctional chiral amides **75a,b** containing proline and α,α-diphenyl-(*S*)-valinol fragments [90] and IL-modified 1,2-bis(prolinamido)cyclohexanes **76a,b** [91] and explored them in asymmetric aldol reactions. We had assumed that these catalysts, which determine the transition state geometry through the hydrogen bond network formation [92], could combine high enantioselectivity with recoverability (Scheme 22.25). Hydrophilic bromides **75a** and **76a** as well as hydrophobic hexafluorophosphates **75b** and **76b** catalyzed the reactions in the presence of water. Nevertheless, the latter, being poorly soluble in water, exhibited higher activity in reagents/water two-phase systems. Both cyclic and linear ketones reacted with aromatic and heteroaromatic aldehydes in the presence of hexafluorophosphates **75b** and **76b** under

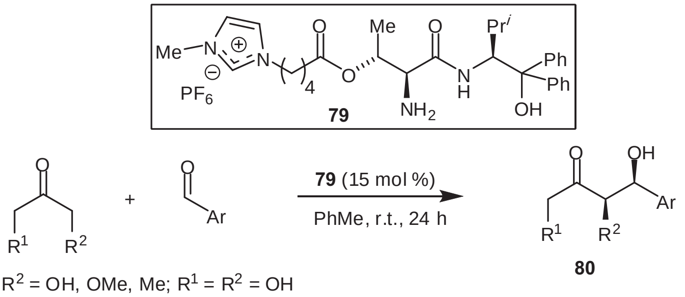


75: An = Br (a), PF6 (b)
76: An = Br (a), PF6 (b)
75b or 76b
(5-10 mol%)
H2O (25-100 equiv)
77: 63-99%, dr 93:7 - 99:1
78-99% ee (anti)
78: 48-99%, 40-97% ee
X = CH2, O, S; R = n-C3H7, n-C6H13, cyclo-C3H5, Bn, CH2OMe;
Ar = C6H4X (X = 2-NO2, 4-NO2, 4-CN, 4-CO2Me, 4-F, 3-OPh),
C6F5, 2-naphthyl, 2-furyl, 2-thienyl, 2-pyridyl

Scheme 22.25 Aldol reactions catalyzed by IL-supported prolinamides in the presence of water.

the heterogeneous conditions to give corresponding aldols **77** and **78** with high regio-, *anti*-diastereo-, and enantioselectivities; the reactions were also easily scalable. Yet the catalytic activity of amide **75b** declined significantly after the third regeneration, presumably because of catalyst leaching into the organic solvent during product extraction, whereas catalyst **76b**, having a less lipophilic hydrogen-donating 1,2-diamidocyclohexane fragment, could be recovered and reused at least ten times without any decrease in reaction rate or selectivity.

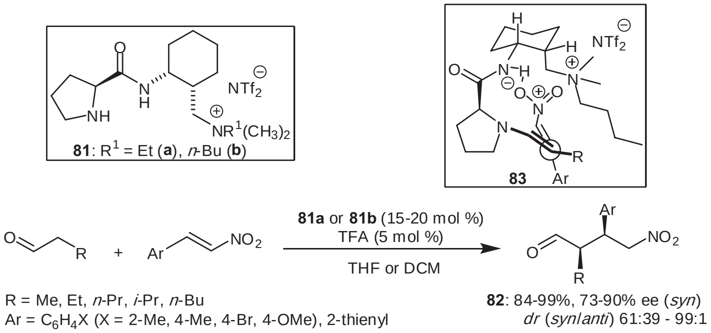
Recently, (*S*)-threonine derived CIL **79** containing the α,α-(*S*)-diphenylvalinol unit was synthesized by our research team [93]. Aldol reactions in the presence of this primary amino acid-derived organocatalyst had an unusual *syn*-diastereoselectivity. The best results were attained in toluene, where the corresponding *syn*-aldols **80** were generated in high yields (up to 99%) and with high diastereo-(*syn* : *anti* up to 97 : 3) and enantioselectivity (up to 99% ee) maintained over three reaction cycles (Scheme 22.26). The prepared compounds are valuable intermediates for the synthesis of polyols with the *syn*-configuration of hydroxy groups, which are structural units of carbohydrates and some other natural compounds.



R^1 = H, R^2 = OH, OMe, Me; R^1 = R^2 = OH
Ar = C_6H_4X (X = 2-Cl, 2-NO_2, 3-OPh, 4-F, 4-NO_2, 4-CHO, 4-CO_2Me, 4-OMe), 2-naphthyl, 2-thienyl

Scheme 22.26 CIL **79**-catalyzed *syn*-aldol reactions.

In 2010, Hirose and coworkers synthesized chiral ammonium ionic liquids **81a** and **81b** containing a prolinamide unit from commercial (+)-*cis*-2-benzamidocyclohexane-carboxylic acid and examined them as catalysts in asymmetric Michael reactions between enolizable aldehydes and β-nitrostyrene derivatives [94]. Both compounds efficiently catalyzed these reactions in organic solvents in combination with an acidic additive (TFA) to afford corresponding *syn*-adducts **82** in high yields and with the moderate to high diastereomeric ratio and enantiomeric excess (Scheme 22.27). The bulky IL group and hydrogen bonding between amide NH and the nitro group of nitro olefin in the enamine transition state (**83**) are considered to be important for high catalytic activity and stereoselectivity. In addition, possible ionic attraction between the ammonium cation and the nitro group of the substrate should also contribute to stabilization of the intermediate. Unfortunately, CIL catalysts **81a** and **81b** failed to be efficiently reused more than once, as after the first cycle their catalytic activity decreased significantly.

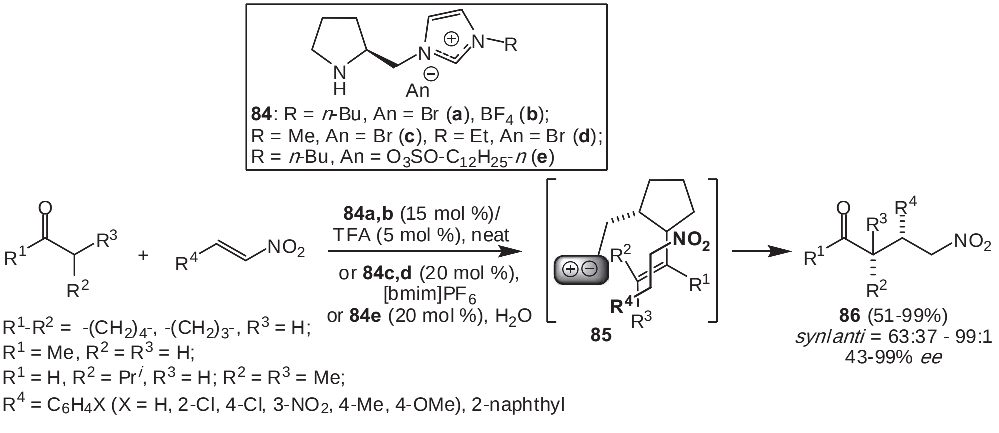

NH
N H
NTf2
NR1(CH3)2
81: R1 = Et (a), n-Bu (b)
H
H
NTf2
O
N–H
O
O
N
N
N
R
83
Ar
81a or 81b (15-20 mol %)
TFA (5 mol %)
THF or DCM
O
R
+
Ar
NO2
Ar
NO2
O
R
R = Me, Et, n-Pr, i-Pr, n-Bu
Ar = C6H4X (X = 2-Me, 4-Me, 4-Br, 4-OMe), 2-thienyl
82: 84-99%, 73-90% ee (syn)
dr (syn/anti) 61:39 - 99:1

Scheme 22.27 CIL **81**-catalyzed Michael addition of aldehydes to substituted *trans*-β-nitrostyrenes.

22.3.2.3 Pyrrolidine-Sourced Ionic Organocatalysts

22.3.2.3.1 Catalysts with the Ionic Appendix at Position 2 of the Pyrrolidine Ring

The synthesis of chiral ILs bearing a pyrrolidine (not proline) unit, along with their application in the asymmetric organocatalysis, was pioneered by Chinese chemists in 2006. Cheng and coworkers succeeded in synthesizing, from proline, the very simple compounds **84a,b** that incorporated a chiral pyrrolidine fragment tagged to the alkylimidazolium cation. They found that the compounds (15 mol%) combined with trifluoroacetic acid (TFA) (5 mol%) were able to very efficiently catalyze asymmetric Michael reactions involving a broad range of donors (ketones and aldehydes) and acceptors (α-nitroalkenes) to give Michael adducts **86** in high yields (up to 99%) and with high *syn*-diastereoselectivity (*syn* : *anti* up to 99 : 1) and enantioselectivity (up to 99% ee) [95]. The authors explained the results in terms of the formation of the acyclic synclinal transition state, syncl-TS (**85**), in which the ionic group selectively shielded the *Si*-side of the enamine double bond, thus orienting the nitroalkene attack in the *Re*-*Re* direction (Scheme 22.28).


N H
N
N–R
An
84: R = n-Bu, An = Br (a), BF4 (b);
R = Me, An = Br (c), R = Et, An = Br (d);
R = n-Bu, An = O3SO-C12H25-n (e)
O
R1
R3
R2
+
R4
NO2
84a,b (15 mol %)/
TFA (5 mol %), neat
or 84c,d (20 mol %),
[bmim]PF6
or 84e (20 mol %), H2O
R1-R2 = -(CH2)4-, -(CH2)3-, R3 = H;
R1 = Me, R2 = R3 = H;
R1 = H, R2 = Pri, R3 = H; R2 = R3 = Me;
R4 = C6H4X (X = H, 2-Cl, 4-Cl, 3-NO2, 4-Me, 4-OMe), 2-naphthyl
NO2
R2
R1
R4
R3
85
O
R1
R3
R4
NO2
R2
86 (51-99%)
syn/anti = 63:37 - 99:1
43-99% ee

Scheme 22.28 Pyrrolidine derivatives tagged to alkylimidazolium cations and their use as organocatalysts in asymmetric Michael reactions of carbonyl compounds with α-nitroalkenes.

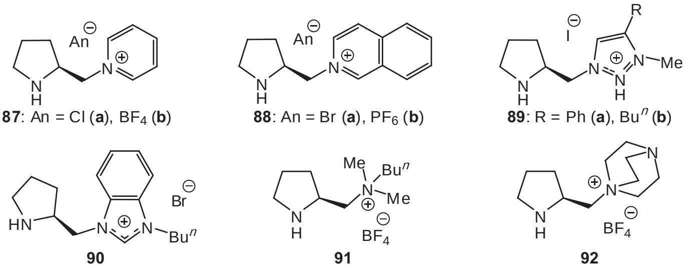
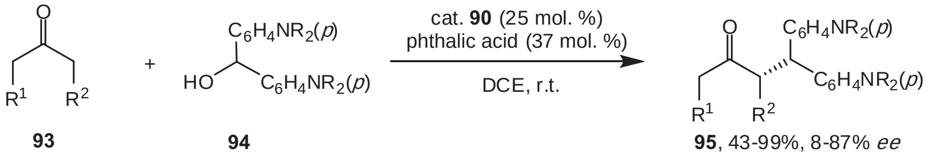

87: An = Cl (**a**), BF_4 (**b**)
88: An = Br (**a**), PF_6 (**b**)
89: R = Ph (**a**), Bu^n (**b**)
90
91
92

Figure 22.6 Organocatalysts bearing a pyrrolidine unit tagged to pyridinium, isoquinolinium, 1,2,3-triazolium, benzimidazolium, or tetraalkylammonium cations.

In parallel, Xu and coworkers discovered that in the presence of similar IL-tagged pyrrolidines **84c,d** the reaction proceeded nearly as efficiently in the [bmim][PF_6] medium, so there is no need to deliver the acid co-catalyst (TFA) to the system because this role is obviously played by the IL fragment [96]. Catalysts **84a,b** were recovered from the reactant medium by precipitation with ether, while the **84c,d**/IL systems were reused after product extraction without further purification. Four reaction cycles of catalysts **84** did not reduce reaction diastereo- and enantioselectivities; however, the recovered catalysts gradually became less active with each cycle. Surfactant-type IL-supported asymmetric organocatalyst **84e** synthesized by Luo and Cheng and coworkers in 2006 catalyzed Michael addition to nitroalkenes with high stereoselectivities in water without any additives [97].

The cation fragment nature exerts negligible impact on selectivity of the Michael reactions that involve enamine intermediates and commonly the stereochemical outcome remains high. Indeed, pyrrolidine derivatives (Figure 22.6) containing pyridinium **87a,b** [98], isoquinolinium **88a,b** [99], 1,2,3-triazolium **89a,b** [100], benzimidazolium **90** [101], and linear **91** [102] or cyclic **92** [103] quaternary ammonium cations in combination with various anions proved efficient catalysts of asymmetric additions of carbonyl compounds to α-nitro alkenes. Desymmetrization of prochiral 4-substituted cyclohexanones can be achieved by analogy [101]. The reaction efficacy was similar under neat conditions in the presence of acidic additives (catalysts **87**, **89**, **90**, **91**) or in the IL medium (commonly in [bmim]BF_4) (catalysts **88a,b**, **92**).

CIL **90** in combination with phthalic acid efficiently catalyzed asymmetric reactions of cyclic ketones **93** with diarylhydroxymethane derivatives **94**, affording alkylation products **95** with yields from moderate to high and a broad range of enantiomeric excess (8–87% ee) [104] (Scheme 22.29). Presumably, ketone **93**-derived enamines and alcohol **94**-sourced diarylmethyl cations were intermediates in these reactions. Desymmetrization products **95** [R^1, R^2 = $CH_2CH(R)CH_2$] were selectively [dr (trans : cis) >99 : 1, ee up to 87%] prepared from 4-substituted cyclohexanones in nearly quantitative yields. CIL catalyst **90** used here could be recycled by precipitation with diethyl ether and used directly in the next run with similar activity, diastereoselectivity, and enantioselectivity in three reaction cycles.



93, **95**: R^1, R^2 = $-CH_2-$, $-(CH_2)_3-$, $-CH_2XCH_2-$ (X = O, S, NMe), $-CH_2CHRCH_2-$
(R = Me, Et, *t*-Bu, *t*-Pent, Ph, 4-BrC_6H_4, N_3, OH, AcO, 4-BrC_6H_4COO)
94, **95**: R = Me, Et; R, R = $-(CH_2)_2O(CH_2)_2-$

Scheme 22.29 Reactions between ketones and alcohol acceptors in the presence of CIL **90.**

In 2008, Chinese researchers attempted to increase the performance and recoverability of IL-supported catalysts by attaching the imidazolium tag they contained to a polymeric matrix, for example, polystyrene or silica gel, or to the 1,2,3-triazolyl-derived spacer group (Figure 22.7). Immobilized catalysts **96** [105], **97** [106], **98a** [107], and **98b** [108] of these types were highly efficient in asymmetric reactions of cyclic ketones with β-nitrostyrene derivatives under neat conditions to give the corresponding Michael adducts with a diastereomeric excess and enantiomeric purity not inferior to those attained under the action of catalysts **84a–d.** Catalysts **96–98** were readily separated from the products and efficiently catalyzed Michael reactions up to eight times without a decrease in diastereo- and enantioselectivity.

Headley and coworkers developed sulfamides **99a** [109], **99b** [110], and **100** (Figure 22.8) [111] bearing the (*S*)-pyrrolidine and 1,3-dialkylimidazolium structural units, which exhibited a high catalytic performance in asymmetric Michael additions of enolizable aldehydes or ketones to β-nitrostyrene derivatives. Sulfamide **100** [111] and CIL-catalyst **101** synthesized by Xu and coworkers [112], in

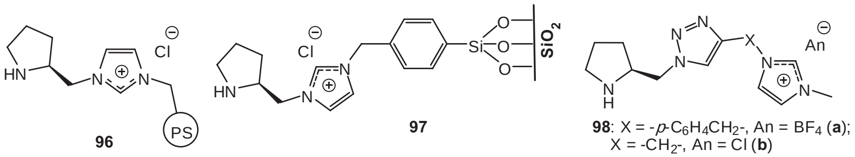


Figure 22.7 Pyrrolidine-derived organocatalysts bearing the imidazolium unit attached to a polymeric matrix or triazolyl fragment.

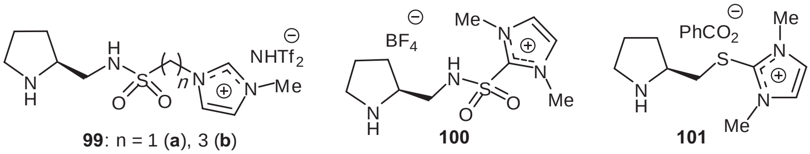
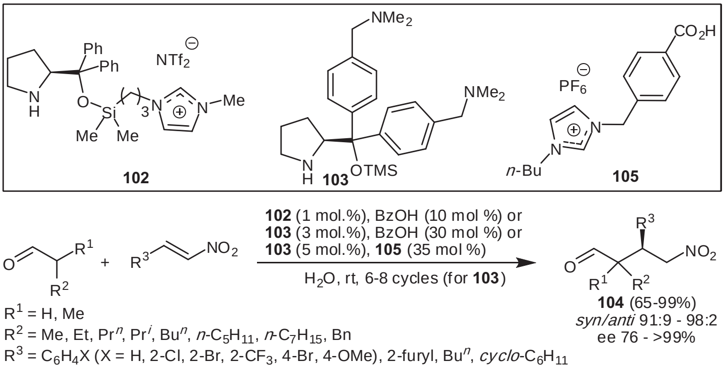


Figure 22.8 Pyrrolidine organocatalysts attached to the imidazolium cation by sulfur-containing linkers.

which the sulfur atom of the linker was attached to position 2 of the 1,3-dialkylimidazolium fragment, also acted as efficient catalysts of Michael reactions involving cyclic ketones. Compounds **99–101** could be recovered from the reaction mixture and reused 3–7 times without a significant loss of catalytic activity and stereoselectivity.

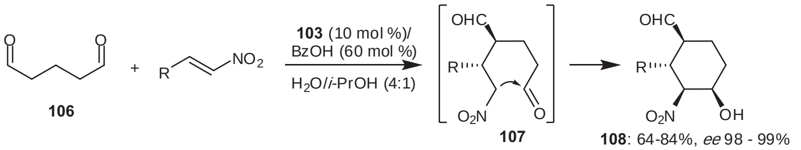
Recently, a series of IL-modified versions of O-TMS-α,α-diarylprolinol Jørgensen–Hayashi catalysts, which efficiently catalyze a wide range of asymmetric reactions due to their ability to activate carbonyl compounds by the formation of either the enamine or iminium ion, have been synthesized. The ionic fragments were incorporated in the catalyst structure by a linker tagged to the silica atom of the siloxy group or aryl groups or to the pyrrolidine unit. In 2009, Lombardo with coworkers developed imidazolium-tagged diphenylprolinol silyl ether **102** bearing a siloxy group attached to the cation unit [113], and a year later Ni with co-authors synthesized O-TMS-α,α-diarylprolinol derivative **103** containing *N,N*-dimethylamino-methylated aryl groups that are easily transformable into the corresponding tetraalkylammonium IL fragments by simple protonation [114]. Compound **102** or O-TMS-α,α-diarylprolinol **103** in combination with a Brønsted acid efficiently promoted the asymmetric Michael addition of aliphatic aldehydes to nitroalkenes. Reactions in the presence of catalyst **102** could be carried out in a broad variety of solvents, including organic solvents, ionic liquids, or water, whereas a water-soluble **103**/BzOH catalytic system exhibited a high catalytic performance in the aqueous environment to afford Michael adducts **104** with excellent diastereo- (dr *syn* : *anti* up to 98 : 2) and enantioselectivity (>99% ee) at low catalyst loadings (0.25–5 mol%) and using just a slight excess of aldehydes (1.2–2 equiv.) (Scheme 22.30). The catalytic system **103**/BzOH showed fairly good recyclability. Once the reaction was completed, the Michael adduct was extracted by organic solvents and the recovered solution of **103** in the aqueous phase was used again for the next cycle directly by addition of fresh portions of benzoic acid and reagents. This procedure could be repeated five times, then the catalyst activity


Ph
Ph
NTf2
N
H
O
Si
Me
Me
3
N
⊕
N
Me
102
NMe2
NMe2
N
H
103
OTMS
PF6
CO2H
⊕
N
N
n-Bu
105
O
R1
R2
+
R3
NO2
102 (1 mol.%), BzOH (10 mol %) or
103 (3 mol.%), BzOH (30 mol %) or
103 (5 mol.%), 105 (35 mol %)
H2O, rt, 6-8 cycles (for 103)
O
R3
NO2
R1
R2
104 (65-99%)
syn/anti 91:9 - 98:2
ee 76 - >99%
R1 = H, Me
R2 = Me, Et, Prn, Pri, Bun, n-C5H11, n-C7H15, Bn
R3 = C6H4X (X = H, 2-Cl, 2-Br, 2-CF3, 4-Br, 4-OMe), 2-furyl, Bun, cyclo-C6H11

Scheme 22.30 CIL **102** and protonated O-TMS-α,α-diarylprolinol **103**-catalyzed asymmetric Michael reaction of aldehydes with nitroalkenes.

dropped significantly while the optical purity of products **104** was retained at the same level [114]. In 2011, Ni and Headley with coworkers succeeded in extending the efficient life of catalyst **103** up to 7–8 cycles by replacement of the BzOH additive with IL-supported Brønsted acid **105** [115]. The **103/105** catalytic system, being progressively deactivated, could be used 12 times without a significant loss of stereoselectivity.

A protonated O-TMS-diphenylprolinol **103**/BzOH catalytic system was used by Ni *et al.* in an asymmetric domino Michael/Henry reaction in an aqueous medium. Chiral Michael adducts **107** generated *in situ* from pentane-1,5-dial (**106**) and β-nitrostyrene derivatives spontaneously underwent an intramolecular Henry reaction under the proposed conditions to afford 3-substituted 2-nitro-4-formylcyclohexanols **108** containing four stereocenters in moderate to high yields and with almost complete enantioselectivity (Scheme 22.31) [116]. The catalyst could be recycled at least four times, with only a slight reduction in yields and diastereoselectivity.



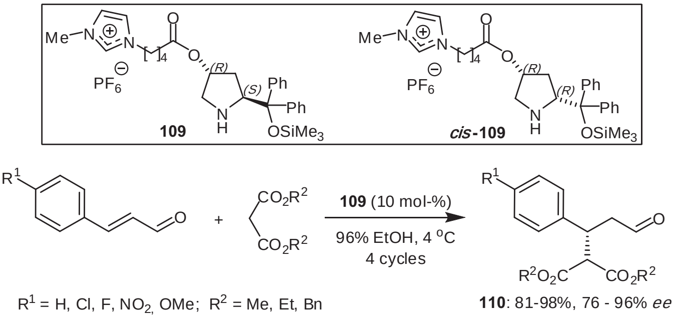
107, 108: R = Ph, XC_6H_4(X = 4-MeO, 3-MeO, 4-Br, 3-Br, 4-NO_2, 4-Me), 2-furyl, 3,4-methylenedioxy-C_6H_4

Scheme 22.31 Domino Michael/Henry reaction catalyzed by **103**/BzOH.

The O-TMS-diphenylprolinol **103**/BzOH catalytic system is also applicable as an organocatalyst of Michael reactions of nitroalkanes with α,β-enals in aqueous medium [117]. However, functionalized task-specific ionic liquids incorporated in the chiral-pyrrolidine unit, apart from being very efficient and versatile organocatalysts of Michael and some other asymmetric reactions, show much worse behavior in asymmetric aldol reactions, where their performance is inferior to IL-supported catalysts bearing the α-amino acid fragment [118].

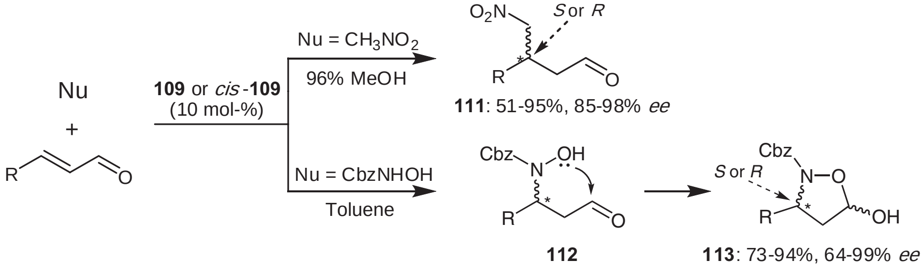
22.3.2.3.2 **Catalysts with the Ionic Appendix at Position 3 of the Pyrrolidine Ring**

In organocatalytic Michael reactions of carbon acids with α,β-unsaturated carbonyl compounds the catalyst activates the latter through the formation of iminium cations with them. There have been few recoverable organocatalysts developed for these reactions so far, presumably because active iminium cations readily undergo side transformations that deactivate the catalyst. We succeeded in developing a recoverable organocatalyst for asymmetric Michael reactions of this type by tagging a α,α-diphenylprolinol derivative bearing the second hydroxyl group at position 3 of the pyrrolidinium ring to the *N*-methylimidazolium cation with the help of an ester spacer group [119]. In the presence of chiral IL **109** bearing the O-TMS-α,α-diphenylprolinol fragment dialkyl malonates reacted with cinnamaldehyde derivatives in EtOH to give corresponding adducts **110** in high yields (up to 98%) and with high enantioselectivity (up to 96% ee) (Scheme 22.32). Noticeably, compound **109** facilitated the formation of the key intermediate in the synthesis of an effective antidepressant drug (–)-paroxetin–adduct **110** with R^1 = F and R^2 = Bn–and increased its ee value. Catalyst **109** can be reused four times without any fall in activity and process enantioselectivity.



Scheme 22.32 Enantioselective Michael additions of dialkyl malonates to substituted *trans*-cinnamaldehydes catalyzed by **109.**

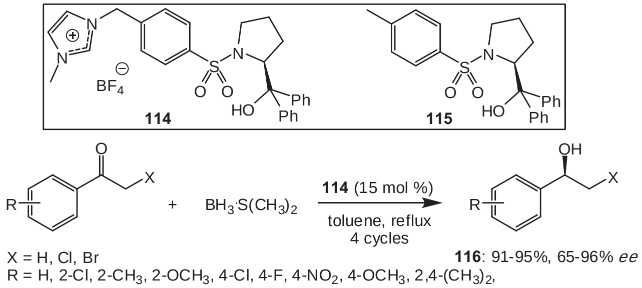
CIL **109** and the isomeric compound *cis*-**109** proved to be efficient catalysts of the asymmetric addition of other C- or N-nucleophiles to α,β-unsaturated aldehydes. Nitroalkanes reacted with α,β-enals in 96% MeOH or toluene in the presence of these catalysts to afford (*S*)- or (*R*)-enantiomers of the corresponding Michael adducts **111** in high yield and with moderate to high enantiomeric purity (Scheme 22.33) [120]. Reactions of N-protected hydroxylamines with α,β-unsaturated aldehydes in toluene gave chiral 5-hydroxy-3-arylisoxazolidines **113**, the products of spontaneous intermolecular acetalization of *in situ* generated corresponding Michael adducts **112** under the proposed conditions [121]. Among the prepared γ-nitro aldehydes **111** are key intermediates for the synthesis of the most active (*R*)-enantiomers for medications, such as phenibut, baclophen, and rolipram, for some CNS disorders, whereas chiral 5-hydroxy-3-arylisoxazolidines **113** are valuable intermediates in the synthesis of chiral β-amino acids, which serve as key motifs of natural compounds and precursors for the preparation of β-lactam antibiotics and β-peptides. Note that although catalysts **109** and *cis*-**109** are not optical antipodes (*S*)- and (*R*)-enantiomers of products **111** and **113** have nearly equal ee magnitudes, apparently due to the major stereodifferentiating effect of the stereocenter C5. The catalyst sustainability depended on the reaction conditions. In air catalyst **109** became less active after the third recovery cycle whereas in argon both activity and enantioselectivity remained the same over ten cycles due to inhibition of oxidation side reactions that poisoned the catalyst (ESI-MS data) [122].



Scheme 22.33 CIL **109**-catalyzed asymmetric reactions of C- and N-nucleophiles with α,β-enals.

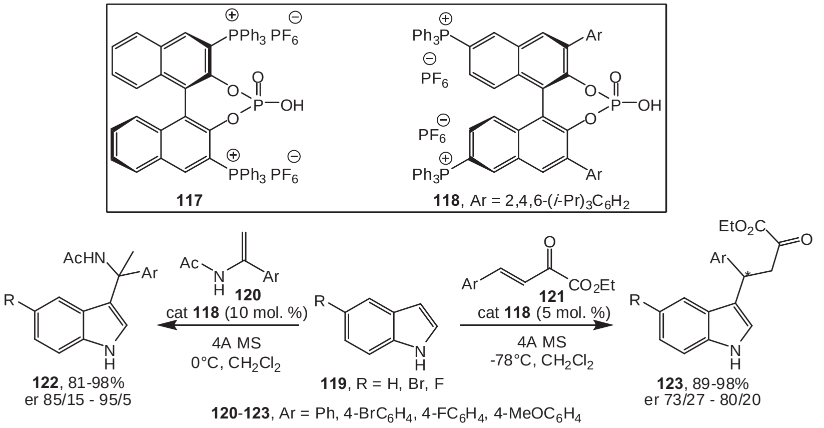
22.3.2.4 **Other Organocatalysts Bearing Ionic Groups**

Liang *et al.* tagged a prolinol sulfonamide unit to the methylimidazolium fragment and used IL catalyst **114** in the enantioselective reaction of ketones with $BH_3{\cdot}SMe_2$ [54]. Reduction of acetophenone derivatives in refluxing toluene in the presence of 15 mol% of catalyst **114**, which had presumably formed a chiral hydrogen-bonding complex with the reducing agent, provided the corresponding alcohols **116** in 91–95% yield and with a moderate to high enantiomeric excess (Scheme 22.34). In the case of unsubstituted acetophenone (R = X = H), the enantioselectivity was 7% higher under the proposed conditions than in the presence of non-supported catalyst **115.** This observation indicated that the ionic liquid moiety played an active role in the reaction. In addition, CIL catalyst **114** could be easily separated from the products and recycled, though the enantioselectivity was reduced by 8% in the fourth cycle.



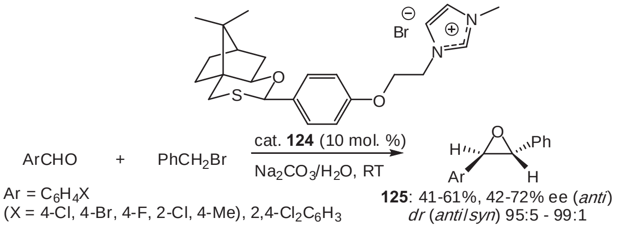
Scheme 22.34 Asymmetric reduction of prochiral ketones catalyzed by CIL **114.**

In 2011, Hermeke and Toy synthesized phosphonium ion-tagged chiral phosphoric acids **117** and **118** bearing a BINAP core and examined them as recoverable organocatalysts in Friedel–Crafts alkylation of indoles [55]. The phosphonium tag position in the catalysts was crucial for the reaction outcome. Compound **117** with the tags at positions 3 and 3′ of phosphoric acid, where they served as space-blocking groups, failed to catalyze the reactions. However, a shift of the phosphonium ion groups to positions 6 and 6′ produced efficient and enantioselective catalyst **118.** In the presence of this catalyst (5–10 mol%), various indoles **119** reacted with enamides **120** or β,γ-unsaturated α-ketoesters **121** under mild conditions to produce corresponding alkylation products **122** and **123** with high yields and from moderate to high enantiomeric ratios (Scheme 22.35). As assisted by the phase tags, chiral catalyst **118** was easily removed at the end of the reactions and could be reused several times, albeit with somewhat decreased efficiency and enantioselectivity.



Scheme 22.35 Phosphonium ion-tagged chiral phosphoric acids **117** and **118** and their use in enantioselective Friedel–Crafts alkylations of indole derivatives.

In 2009, Liu and Huang with coworkers communicated a synthesis of interesting sulfur-functionalized chiral ionic liquid **124** bearing a chiral borneol motif tagged to the imidazolium cation that exhibited promising catalytic activity in an epoxidation reaction of aromatic aldehydes with benzyl bromide in water [56]. In the presence of 10 mol% of catalyst **124**, the corresponding *trans*-epoxides **125** were prepared in reasonable yields (41–67%) with excellent diastereoselectivity (dr = 95 : 5–99 : 1) and moderate enantioselectivities ranging from 42% to 72% ee (Scheme 22.36). Hydrophilic catalyst **124**, which is poorly soluble in diethyl ether,



⊖
Br
⊕
N
N
O
S
O
ArCHO + PhCH2Br
cat. 124 (10 mol. %)
Na2CO3/H2O, RT
O
H
Ph
Ar
H
Ar = C6H4X
(X = 4-Cl, 4-Br, 4-F, 2-Cl, 4-Me), 2,4-Cl2C6H3
125: 41-61%, 42-72% ee (anti)
dr (anti/syn) 95:5 - 99:1

Scheme 22.36 Asymmetric addition of benzyl bromide to aromatic aldehydes catalyzed by **124**.

could be separated from products **125** and reused five times without a remarkable decrease in yields and enantioselectivities. The authors consider the proposed catalytic synthesis of **125** to be the first asymmetric epoxidation via the ylide route in pure water.

22.4
Conclusion

Information reviewed in this chapter highlights the many opportunities opened up by ionic liquids and their congeners as solvents and chiral catalysts in the asymmetric organocatalysis. ILs dissolve organocatalysts of various types, particularly amino acid-derived organocatalysts, which are poorly soluble in hydrocarbons and organic ethers. They enable us to perform asymmetric reactions under homogeneous conditions and at the same time facilitate product separation and catalyst recovery, though in some cases a decrease in selectivity is observed. Several efficient non-covalent immobilization strategies that significantly reduce the required amount of IL are based on the ability of ionic liquid monolayers supported on silica or polymer matrixes to act as an immobilization phase for the catalyst. Of special note is ion-pair immobilization of proline on ionic liquids. Organocatalysts, which covalently incorporate the ionic group (normally a cation) and can be considered as chiral ionic liquid catalysts, have aroused growing interest in asymmetric synthesis. Stereocenters and ionic liquid moieties present in these small molecules provide unprecedented opportunities to improve their catalytic efficiency and recyclability in asymmetric synthesis.

Despite tremendous success in the use of ionic liquids as solvents and supports for asymmetric organocatalysts, this area of research is still in its infancy. Though ionic liquids are generally considered as “green solvents” this statement has recently been called into question by several groups, clearly showing that not all ILs fall into this category and that a detailed evaluation of remote ecological and toxicological risks that may be caused by their use the in laboratory and, especially, in chemical industry is still required [123]. Development of a third generation of ILs, in particular derived from biorenewable raw materials [124], which would cover these ecological gaps while retaining many (or all) of the advantages of ILs as tailored solvents is becoming essential. Most known IL-supported catalysts are limited in activity, selectivity, and scope. Rational explanations of experimental results obtained in this area have so far been rare. Future research should focus on the study of the mechanistic roles of ionic liquids in organocatalysis by both theoretical (DFT calculations) and experimental methods. Several important fundamental issues may be addressed with the help of IL-modified catalysts: their transformations can be easily tracked by spectral techniques (NMR, ESI-MS, etc.), thus providing useful information about intermediates that are generated in the main catalytic cycle and of undesirable side processes that ultimately poison the catalysts [122, 125]. The creation of CILs with improved catalytic performance and chemical stability for a broad range of enantioselective transformations, including continuous processes, remains crucial for industrial application of organocatalysis. However, the activity of research teams in the frontier area, where ionic liquids and organocatalysis merge, underlies the likelihood of breakthrough discoveries and important practical applications in this fascinating field of research.

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23
Polymer and Mesoporous Material Supported Organocatalysts

Tor Erik Kristensen and Tore Hansen

23.1
Introduction

From the 1930s and onwards, and then especially following the Second World War, the field of chemistry and chemical technology underwent a spectacular revolution with respect to macromolecular science [1]. This petrochemical and polymer revolution was initially driven by the development of engineering polymers and associated production technology on bulk scale, mainly intended for various kinds of construction materials. However, this period also witnessed the birth and widespread utilization of certain polymerization techniques for the preparation of various polymer particles, methodology that would later prove essential in numerous fields at the research frontier. As this development was mainly lead by industrial laboratories in chemical companies, the utilization of such polymer products as part of more academically oriented research took considerable time. The first research using the principle of active polymer-supported chemical entities, emerging from the mid-1930s to early 1950s, was oriented towards ion-exchange resins [2]. Several of the archetypical polymer resins, such as beaded and crosslinked polystyrene resin, originate from this period, and were then primarily developed by chemical companies. Much of this early history of suspension and emulsion polymerization technology can be located in two famous publications by Hohenstein and Mark [3].

As the key contributions during this first period of polymer science originated from industrial chemists, the real significance of these discoveries first passed by relatively unnoticed. The first work that really caught the attention of the academic community was the now momentous breakthroughs of Robert B. Merrifield and Robert L. Letsinger in the late 1950s and early 1960s [4, 5]. Both Merrifield and Letsinger were initially occupied by solid-phase peptide synthesis, but Letsinger later left peptide synthesis to Merrifield and went on to pioneer solid-phase oligonucleotide synthesis [4, 5].

After the spread of solid-phase synthesis during the 1960s, the use of polymer supports was later extended to both reagents and catalysts. In 1973, Kagan and coworkers introduced the first polymer-supported chiral complex, a rhodium

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catalyst for asymmetric hydrogenation [6]. Especially, the late John Kenneth Stille and his coworkers dominated this first period of polymer-supported chiral catalysis in the 1970s and 1980s, research centered on organometallic catalysts [7]. The field of solid-supported chiral catalysts consequently experienced rapid growth and has now been extensively reviewed [8]. However, the focus of these treatments is usually the catalytic activity and selectivity of the anchored catalysts. Synthetic strategies for the actual preparation of such polymer-supported catalysts have seldom been reviewed. As we believe cost-issues to be the limiting factor for the widespread utilization of solid-supported catalysts in the everyday activities of the laboratory synthetic chemist, we have recently reviewed the field of both polymer-supported organometallic chiral catalysts and chiral organocatalysts according to a scheme where we divide the field of polymer-supported catalysts as belonging to two general types of synthetic philosophy: solid-supported catalysts prepared according to post-modification strategies where catalysts are anchored onto prefabricated solid supports, and those prepared according to so-called bottom-up strategies where catalyst immobilization and the polymerization of the solid support are closely connected [7, 9]. This chapter presents the field of polymer and mesoporous material supported organocatalysts in a more schematic and overview fashion, probably more in line with traditional and conventional expositions. The reader should consult our previous disclosures to retrieve detailed accounts of the preparation of polymer-supported chiral organocatalysts and analyses of respective strengths and weaknesses of the various synthetic strategies [7, 9].

23.2
Polymer-Supported Organocatalysts

23.2.1
Polymer Resins for Immobilization of Chiral Organocatalysts

Solid supports based on synthetic organic polymers continue to dominate the field of solid-supported chiral catalysts, just as they continue to do so for solid-phase synthesis in general, and in fact have been doing since the time of Merrifield and Letsinger. This is understandable as organic polymers have a natural and tunable conformity with organic solvents. Although a wide variety of polymer resins useful for immobilization of organic catalysts are now commercially available [7–11] they belong almost exclusively to a rather narrow range of general types and are easily categorized thereafter. We will proceed with a very brief overview, but we have provided more extended discussions on this particular point elsewhere and the reader should consult the referenced material for more in-depth information [7–11].

Polymer supports can be classified along several lines, either by physical properties such as its porosity or more according to chemical structure. With regards to physical properties, polymer supports can be of a linear and homogeneously soluble type [poly(ethylene glycol) being the standard example] or of a crosslinked and insoluble type, usually then in the form of spherical beads. The former has found extensive usage, also within organocatalysis, but necessitates precipitation in suitable non-solvents prior to isolation. The latter can be filtered directly out after usage. Crosslinked resins are divided into microporous resins and macroporous resins. The first of these, often referred to as gel-type resins, contain a low level of crosslinker. They consequently have almost no porosity in the dry state and must be swelled in a suitable solvent prior to use (with an accompanying volume expansion) to allow for molecular access. In contrast, macroporous resins contain substantial quantities of crosslinker, have much larger and more accessible pores than gel-type resins, and they maintain the porosity even in the dry state. They can take up solvent with minor volume alterations and are often compatible with a broad range of solvents. However, they give the system of resin and solvent a much more heterogeneous character than for microporous resins, something that has frequently proven detrimental to catalytic activity. As a result, macroporous resins have found relatively limited use within organocatalysis, but they continue to offer exciting opportunities, especially in continuous flow systems since the rigid macroporous resins can handle compression better than gel-type resins.

A more chemical classification of polymer resins is useful as well, and then especially for those of the crosslinked microporous type since they form the largest family of polymer resins that have found use in asymmetric synthesis [9]. They can be roughly classified as either acrylic, styrenic, polyetheral, or a hybrid of two or more of these (by either grafting or crosslinking) [7]. Styrenic networks (Merrifield resin etc.) are both chemically robust and readily available, but they have few handles for functionalization and poor swelling properties in many polar solvents. Acrylic networks (PEGA, CLEAR, etc.) can accommodate a rich chemical functionality and have good swelling properties in many polar solvents, but they are chemically somewhat labile, especially towards strong acids and bases. Polyetheral networks (POEPS, POEPOP, SPOCC, ChemMatrix®, etc.) are both the chemically most inert and have the most favorable swelling characteristics, but they are prohibitively expensive. Styrenic–polyetheral hybrid networks (TentaGel™, ArgoGel™, etc.) also provide many of the same sought after properties of the purely polyetheral networks, but they are also costly. Although microporous resins have been in continuous development since the 1940s, a truly affordable and chemical inert microporous resin with good swelling properties in a broad range of solvents and readily functionalized handles for substrate attachment remains elusive. Clever chemical innovations will hopefully address this in the future as such developments are vital if polymer-supported reagents or catalysts, at least those prepared according to post-modification strategies, are to find widespread use outside a few academic laboratories.

23.2.2
Polymer-Supported Cinchona Derivatives

Since the renaissance of organocatalysis at the turn of the millennium, the origins of organocatalysis have been examined methodically by several of the field's leading researchers. Its history goes back a considerable period of time, and the time span seems to have lengthened as the level of historical scrutiny has increased. This is discussed in other parts of this book, as well as in the references cited there. Indeed, the origins of polymer-supported organocatalysts also stretch back much further than the turn of the millennium. Many of these pioneering contributions will be detailed chronologically as part of this and later sections. However, just as for organocatalysis in general, the subfield of solid-supported organocatalysis witnessed an analogous dramatic surge of contributions in the years following 2000. The work published in the first decade of the millennium has now been comprehensively reviewed from several points of view, both by ourselves and by many others [7, 9, 12]. These references can advantageously be consulted for details, and this chapter will provide a schematic overview to guide newcomers in the field (and hopefully some of its more well-known practitioners as well) to the relevant literature.

Historically, the first immobilizations of cinchona derivatives on polymer resins are the first immobilizations not only of organocatalysts but belong also to the absolute pioneering era of polymeric immobilization in general.[1] The cinchona alkaloids quinine, quinidine, cinchonine, and cinchonidine have fascinated scientists from disparate fields of chemistry for well over a century. While cinchonine and cinchonidine do not contain the aromatic methoxy functionalities present in quinine and quinidine, the cinchona derivatives can therefore only in general be chemically anchored to solid supports through their secondary alcohol, terminal olefin, or tertiary amine. The simple immobilization of cinchona derivatives via their secondary alcohol or tertiary amine by simple procedures such as straightforward alkylation of chloromethylated Merrifield resin has been reported regularly in the literature since the 1980s [13], but provides comparatively little of generic interest for the field as a whole, and such immobilizations frequently interfere or block the catalytic functionalities.

Of more interest are the innovative procedures for immobilization of cinchona alkaloids pioneered by Japanese scientists from the 1970s onwards, procedures using the pendant olefin – methodologies that by and large have maintained their relevance to this day. While an acrylic quinine polymer was already prepared in 1971 [14], it was the quinine-acrylonitrile copolymer **1** (Figure 23.1) prepared by simple free radical copolymerization of quinine and acrylonitrile and published in 1978 that started a long series of investigations into polymer-supported quinine [15]. The catalyst was useful for asymmetric Michael reactions. The elegance of incorporating cinchona derivatives through simple radical copolymerization had a natural appeal and such methodology surged after interest in such derivatives witnessed a rapid growth of interest in the wake of the introduction of the Sharpless methodology for asymmetric dihydroxylation in the late 1980s [7]. This eventually resulted in some controversy as several publications reported copolymerization of cinchona derivatives with methacrylate esters, something that runs counter to well-established polymer chemical principles in that simple allylic derivatives can

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[1] For more on supported cinchona derivatives in general, see References [7–9, 12].

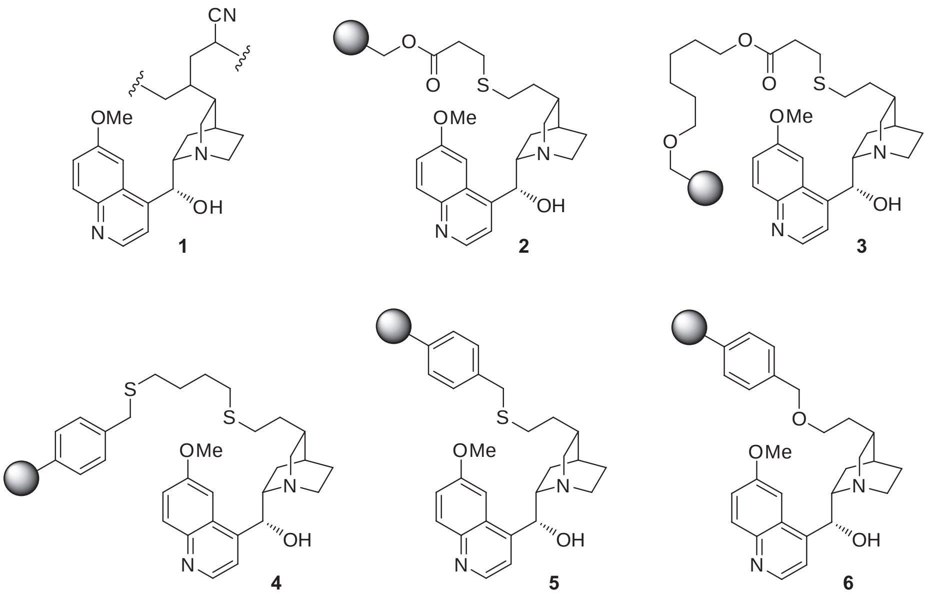


Figure 23.1 Polymer-supported cinchona alkaloids.

only be successfully copolymerized with certain monomers like acrylonitrile, which gives rise to highly electron-deficient free radicals during polymerization, and accordingly not with methacrylates. It was later revealed by Sherrington and coworkers that quinine was actually not covalently bound in such material and could be removed by careful purification [16].

In 1987, again by a Japanese research group, clever thiol-ene chemistry was utilized to prepare supported cinchona catalysts **2** and **3** (Figure 23.1) [17]. The vinyl group of quinine was activated through thiol-ene reaction and the resultant coupling products transformed into allylic derivatives that were copolymerized with acrylonitrile in DMF to give **2** and **3.** Thiol-ene chemistry can also be utilized in a more traditional post-modification approach such as that used by Fréchet and coworkers in 1985 to prepare catalysts **4** and **5** (Figure 23.1), catalysts for Michael additions where the thiol-ene addition is used for coupling cinchona derivatives onto prefabricated, crosslinked, and thiol-modified resins [18]. At the time of writing, thiol-ene chemistry is of course a major field of research, much helped by its conceptual redefinition as a "click" reaction. Synthetic pathways to polymer-supported cinchona derivatives continue to surface in the literature, but the procedures cannot be said to have surpassed the elegance and practicality of the procedures just discussed. A more recent disclosure from 1999 reported catalyst **6** (Figure 23.1), using hydroboration to activate the vinylic bond of a silyl-protected quinine and a chloromethylated Merrifield resin for immobilization, the derivative being anchored by alkylation of the resin by the alcohol resulting from the hydroboration [19]. For quinine and quinidine, the quinoline methoxy substituent (which is not present in cinchonine and cinchonidine) is also a helpful point of entry for immobilization, and such a procedure was reported in 2008 [20].

23.2.3
Polymer-Supported Enamine–Iminium Organocatalysts

In general, literature disclosures detailing polymer-supported enamine–iminium organocatalysts originate after the renaissance of organocatalysis in 2000, but there is at least one particular exception. Already in 1985, a Japanese research group reported supported proline **7** (Figure 23.2), using chloromethylated Merrifield resin as their point of departure [21]. However, this catalyst was only partially successful in the intramolecular aldol reactions that were in focus at the time, and further research had to await the arrival of asymmetric intermolecular aldol reactions after 2000. The first reported procedures in this new era were centered around poly(ethylene glycol) (PEG) bound prolines [9, 22]. Italian researchers at the University of Milan reported extensively on PEG prolines like catalyst **8** (Figure 23.2) in the period 2001–2003, while Chinese research groups later developed PEG catalysts **9** and **10** via more elaborate procedures [9]. These catalysts performed reasonably well in standard organocatalytic aldol reactions, but they compete with

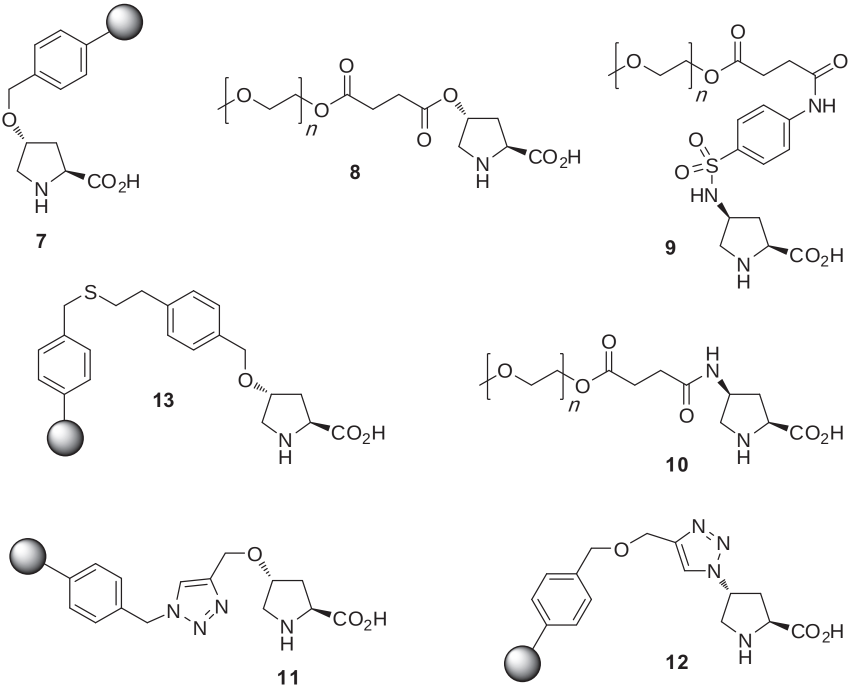


Figure 23.2 Polymer-supported prolines.

difficulty when compared to the supported prolines developed later (using crosslinked supports) because they must be precipitated after reaction using a non-solvent and usually have rapidly eroding catalyst activities and selectivities following recycling. In addition, it is difficult to obtain useful catalyst loadings on the solid support when using PEG for immobilization as the PEG/catalyst ratio must be kept relatively large to allow the solubility properties of PEG to dominate the combined PEG–catalyst species, something that usually is necessary for the facilitated precipitation after reaction.

Probably above all others, it was the work reported by Pericàs and coworkers and Gruttadauria and coworkers from 2006 and onwards that truly accelerated the field of polymer-supported enamine–iminium catalysis to the scope it reached in later years [23, 24]. Pericàs and coworkers used the Cu(I)-catalyzed azide-alkyne cycloaddition to anchor proline derivatives onto a Merrifield resin to give catalyst **11** in 2006, as well as catalyst **12** in 2008 (Figure 23.2), catalysts that are useful even under continuous-flow conditions [23]. Gruttadauria and coworkers used the thiol-ene coupling of styrenic proline derivatives and thiol-modified Merrifield resin to give catalyst **13**, first disclosed in 2007 [24]. These catalysts can perform remarkably well in organocatalytic aldol reactions of benzaldehydes and cyclohexanone, and they attracted widespread attention mainly because under some conditions they can outperform monomeric catalysts, an effect that may perhaps be referred to as "enzyme-like," and is unusual since immobilization usually tends to somewhat deactivate organocatalysts. As the styrenic Merrifield resin is highly hydrophobic while the anchored proline derivatives (especially the triazole ones like in **11** and **12**) are decidedly hydrophilic, the immobilized catalyst in the presence of reactants and water can give rise to pockets inside the resin where special interfacial effects can come into play and affect the catalytic mechanism and reaction outcome [12f].

Despite the impressive catalytic activity and selectivity of catalysts like **11**–**13** and their convenient recycling (they come in the form of crosslinked and spherical beads that can be filtered directly from the reaction mixture), they can only be prepared in rather minute quantities. We wanted to combine the attractive catalytic activity and practicality of such resins with a truly scalable and non-chromatographic synthesis. We approached the issue by first developing a novel direct *O*-acylation of proline [25], a methodology that allowed us to prepare acrylic proline derivatives like **14**–**19** (Figure 23.3) directly on a multigram scale without recourse to chromatography. These building blocks can be used directly in large-scale copolymerizations to give polymer-supported prolines with catalytic activities and selectivities equaling or even surpassing those for catalysts **11**–**13** (Figure 23.2), and the swelling characteristics and catalyst loadings were then tunable by simple adjustment of copolymerization ratios and choice of suitable co-monomers [26]. While derivatives **14**–**17** are hydrophilic and useful in solution homo- or copolymerization, derivatives **18** and **19** are more hydrophobic and can be successfully suspension copolymerized to crosslinked beads [26]. In addition, as *trans*-4-hydroxy-L-proline can be so easily converted into *cis*-4-hydroxy-D-proline directly (Figure 23.4), we

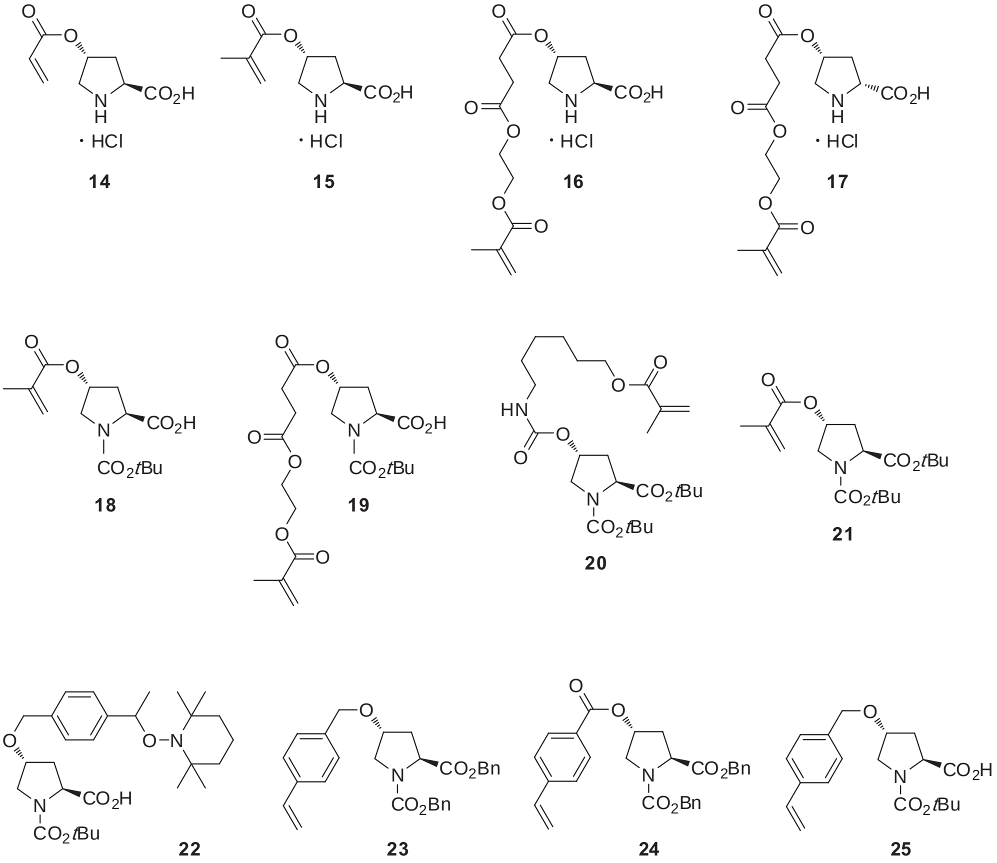


Figure 23.3 Functional monomers for preparation of polymer-supported prolines by copolymerization.

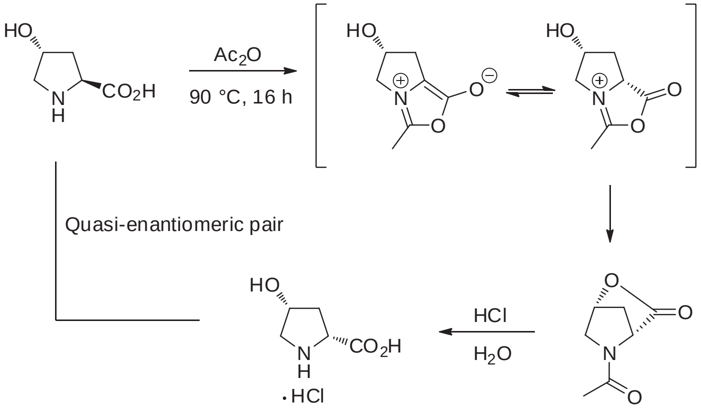


Figure 23.4 Facile interconversion of *trans*-4-hydroxy-L-proline and *cis*-4-hydroxy-D-proline.

were also able to prepare two quasi-enantiomeric series of these catalysts through derivatives like **17**, thereby making it possible to reach both series of enantiomeric reaction products [26b].

The copolymerization strategy for preparation of supported prolines forms the core of bottom-up strategies for polymeric immobilization and has now been comprehensively developed by other scientists [27–31]. Protected acrylic proline derivatives like **20** and **21** have been used in the preparation of both homopolymers and crosslinked systems [27], while nitroxide **22** has been used in nitroxide-mediated polymerization (NMP) [28], but polymers from the latter have not been used in organocatalysis. Furthermore, styrenic prolines **23** and **24** (or its corresponding Boc-protected analog) have been successfully homo- or copolymerized by NMP or reversible addition–fragmentation chain transfer (RAFT) polymerization to give organocatalytically active products in a much more controlled manner than that possible by free radical polymerization [29]. The arrival of controlled forms of radical polymerization in organic synthesis may actually open up entirely new opportunities in the years to come. Very recently, the functional proline monomer **25** has been utilized in a bulk copolymerization together with styrene and divinylbenzene in the presence of porogens (1-dodecanol and toluene) to give macroporous monoliths [31]. This resin proved useful in organocatalytic Mannich additions of ketones to thiazines and oxazines, and this is actually an interesting and rare case of the successful exploitation of a macroporous resin in organocatalysis. Hopefully, more will emerge in the years to come as macroporous structures, as already pointed out, can prove especially useful under continuous-flow conditions due to their resistance towards compression.

The proline-amides form a large family of powerful enamine–iminium organocatalysts, and they have also naturally caught the attention of scientists working in the field of polymer-supported organocatalysts. In particular, Gruttadauria and coworkers, using the same methodology as that used for proline catalyst **13** (Figure 23.2), have developed such systems and studied them in detail [32]. We also developed a family of polymer-bound proline-amides in two quasi-enantiomeric series, catalysts capable of use in preparative chemistry at the gram scale, by straightforward peptide coupling of our supported prolines and phenylglycine-derived amino alcohols [26]. Such systems will not be expanded on further here as they mainly incorporate knowledge developed as part of the immobilization of proline and as such add relatively little to the presentation herein.

The Jørgensen–Hayashi diarylprolinol silyl ethers form a privileged family of enamine–iminium organocatalysts. Probably above all other organocatalysts in this category, their scope of application seems almost limitless. As such, they are particularly attractive targets for efficient immobilization, but at the same time they represent considerable challenges due to their chemically more complex and labile nature. The Jørgensen–Hayashi catalysts share their diarylprolinol structural scaffold with the Corey–Bakshi–Shibata (CBS) asymmetric reduction catalysts, and some Jørgensen–Hayashi catalysts such as diarylprolinol **26** and **27** (Figure 23.5) are in reality silylated versions of CBS precursors intended for the CBS reductions [9, 33]. Also in 2008, German researchers used NMP polymerization and

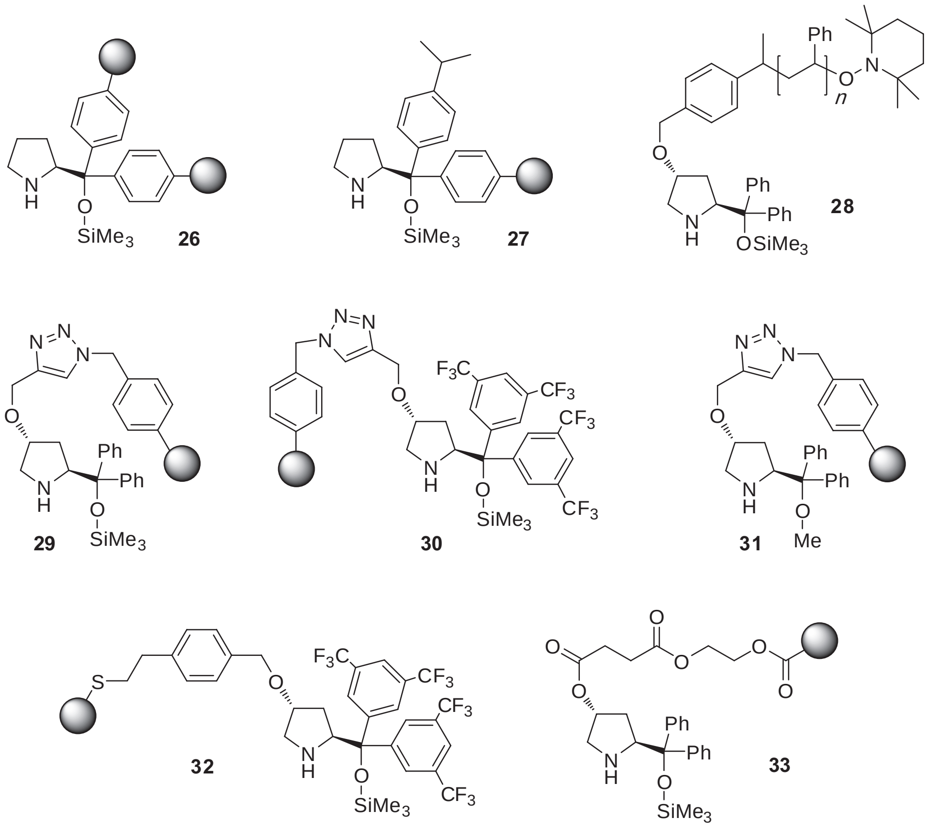
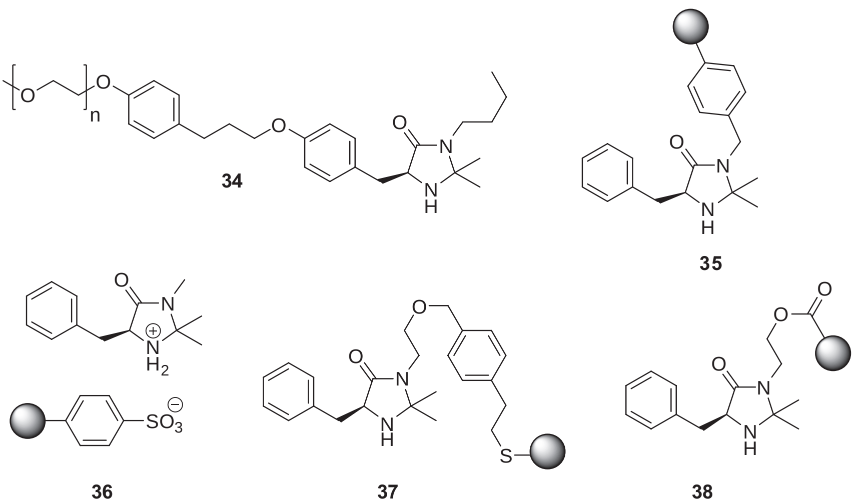


Figure 23.5 Polymer-supported Jørgensen–Hayashi organocatalysts.

electrospinning to give catalyst **28**, a moderately successful catalyst in asymmetric Michael reactions [34].

Pericàs and coworkers have developed several successful immobilized Jørgensen–Hayashi organocatalysts by employing a synthetic strategy very much like that used for proline catalysts **11** and **12** (Figure 23.2) by the same research group [35a–c]. Using a special Cu(I)-catalyst, propargyl diarylprolinol derivatives were attached to azido-modified Merrifield resins via the Cu(I)-catalyzed azide-alkyne cycloaddition to give catalysts **29**–**31** (Figure 23.5). Impressive results have been obtained with these catalysts in asymmetric Michael additions and domino reactions, also under continuous-flow conditions [35a–c]. The same research group has also addressed the issue of recycling of these Jørgensen–Hayashi catalysts, something that is intricate due to the labile nature of silyl ethers in general. Other researchers have utilized the same type of diarylprolinol intermediates and the azide-alkyne cycloaddition to prepare a closely related PEG-linked catalyst [35d]. In 2011, Gruttadauria and coworkers reported the Jørgensen–Hayashi



34 **35** **36** **37** **38**

Figure 23.6 Polymer-supported MacMillan imidazolidinones.

organocatalyst **32** (Figure 23.5), prepared in analogy with their proline catalyst **13** (Figure 23.2), but the immobilized catalyst worked rather poorly in asymmetric α-selenenylations [36].

Extending our previous work on acrylic prolines, we reported a large scale adaptable synthesis of an acrylic polymer-bound Jørgensen–Hayashi diarylprolinol in 2010 [26b]. By synthesizing a suitable acrylic precursor on a robust gram scale, again by taking advantage of a selective *O*-acylation [25], catalyst **33** was obtained by simple copolymerization. In fact, the pursuit of immobilized diarylprolinol silyl ether organocatalysts has led to a particularly interesting equilibrium of post-modification versus copolymerization strategies due to their intermediate complexity.2)

The MacMillan imidazolidinones are definitely one of the most important organocatalysts belonging to the enamine–iminium class. Several notable polymer-supported MacMillan-type catalysts have been reported, and together with proline they were among the first to surface in the literature. PEG-linked catalyst **34** and JandaJel™-bound catalyst **35** (Figure 23.6) were both reported in 2002 [37, 38]. Although supported MacMillan catalysts were reported at an early stage, their development did not advance at the same pace as supported prolines would later do. Catalyst **36**, available by simple ion-exchange reaction using a sulfonated polystyrene resin was reported in 2010 [39]. Gruttadauria and coworkers reported MacMillan catalyst **37** very recently, extending their post-modification system based on the thiol-ene coupling for preparation of polymer-supported organocatalysts [36]. Interestingly, this catalyst was tested in asymmetric

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2) See References [7, 9] for an extended discussion on which points we believe determine whether a catalyst is most suited for immobilization via post-modification or copolymerization.

α-selenenylations and could be recycled successfully at least three times. We extended our system of large-scale adaptable polymer-supported organocatalysts in 2010 by incorporating acrylic MacMillan catalyst **38** (Figure 23.6) in our bottom-up system [26b]. It was prepared by copolymerization of an acrylic MacMillan precursor with PEG-methacrylates and had favorable swelling characteristics, but unfortunately suffered from erosion of catalyst activity/selectivity during reuse. The MacMillan imidazolidinones can be chemically quite labile under certain conditions.

23.2.4
Miscellaneous Polymer-Supported Chiral Organocatalysts

Cinchona derivatives and the enamine–iminium organocatalysts, and then, particularly, proline, proline-amides, the Jørgensen–Hayashi diarylprolinols and the MacMillan imidazolidinones, encompass the bulk of research efforts that have gone into the development of chiral organocatalysts from the 1970s up to present times. As such, the methodology generated from them forms the core of that which has been applied when other polymer-supported chiral organocatalysts have been prepared. They at least form a sort of paradigm that the field is currently working under. Although a comprehensive treatise of other chiral organocatalysts cannot be accommodated within the limited space of this chapter, readers may find them in many of the general references [8, 12].

The research group of Wennemers has studied the organocatalysis of small peptides in much detail [40]. These peptides can be used at very low catalyst loadings under some conditions, and very efficient polymer-supported versions have been developed [7, 41]. The thioureas, pioneered above all by the group of Jacobsen in the USA, are especially promising catalysts that experience an ever-widening field of applications. Polymer-supported versions have been part of it [42], more or less from the beginning, but we will most probably see rapid developments in the years to come. In addition, supported versions of Juliá–Colonna epoxidation catalysts were studied around the time organocatalytic research expanded quickly [43], but the results do not have seemed to have convinced others to undertake more sustained efforts.

One last detail we wish to emphasize at this point is that supported versions of organocatalysts that undertake their catalytic functions by non-covalent activations, such as chiral (thio)ureas and Brønsted acids, do seem to be somewhat underdeveloped at the time of writing. Hopefully, this can be addressed in the future as such catalysts may hold promise of both good catalytic activity and efficient recycling as they may be less susceptible to covalent and irreversible deactivation. Indeed, Rueping and coworkers recently reported a highly efficient and immobilized chiral Brønsted acid by copolymerizing a set of advanced functional monomers with styrenes [7, 44]. In addition, interesting polymer-supported thioureas or proline thiourea catalysts, the latter even in a poly(vinyl chloride) (PVC) immobilized version, have also started to emerge [45].

23.3
Mesoporous-Supported Organocatalysts

23.3.1
Mesoporous Materials for Immobilization of Chiral Organocatalysts

Mesoporous materials are materials that contain pores with a size range between those of the microporous and macroporous materials. By definition, and according to IUPAC recommendations, micropores have widths less than 2 nm, mesopores have widths between 2 and 50 nm, and macropores have widths larger than 50 nm [46]. While such definitions according to pore size are probably necessary for strict classification purposes, here we approach mesoporous materials from a chemically more intuitive and pragmatic point of view, as the actual definitions above do not entail any chemical structures. As detailed in the previous section on polymer resins, microporous polymer resins are gel-like resins that need to swell in a suitable solvent prior to reaction to allow for access of any reactants, while macroporous polymer resins are highly crosslinked and rigid structures that maintain porosity in the dry state and that consequently do not need any solvent swelling to allow pore access. Most mesoporous materials, when analyzed from the viewpoint of how they are utilized in preparation of supported catalysts, perhaps have more in common with the macroporous than the microporous resins, but they are (usually) made out of mineral constituents instead of organic polymers. They are normally rigid materials with a high specific surface area and large pore volumes, usually prepared from mineral oxides like silica, alumina, zeolites, and the like. They contain fine-sized pores smaller than those of macroporous materials, but have some of the same properties. They are compatible with a wide range of solvents as their rigid pore structures do not need swelling to allow molecular access (hence they can also suffer from a very heterogeneous reaction character under use), but they have pore sizes much more like microporous resins and as such can attain higher substrate loadings than those possible for macroporous resins.

Mesoporous materials can have varying degrees of order and disorder in their three-dimensional structures. Although mesoporous materials have considerable history due to their close association with oil refining, the petrochemical industry, and heterogeneous catalysis [47, 48], the use of such materials only really gained momentum in the 1990s when researchers at Mobil Research and Development Corporation disclosed their family of mesoporous solids prepared by calcinations of aluminosilicate gels in the presence of surfactants (liquid-crystal templated mechanism) [49a–d]. These materials possessed regular arrays of uniform mesoporous channels that could be tailored by appropriate choice of reaction conditions. One of these materials, MCM-41 (mobile composition of matter no. 41 or Mobil crystalline material no. 41), has remained extremely popular. In 1998, the field was further strengthened by the disclosure of the preparation of mesoporous silica with periodic 5–30 nm pores, called SBA-15 (Santa Barbara amorphous no. 15) [49e].

In this chapter, we take a very loose and pragmatic view of what we will include under mesoporous material supported chiral organocatalysts. In addition to traditional mesoporous materials like silica, we will take the liberty also to include some chiral organocatalysts supported on such species as nanoparticles and other nanostructured systems. Although such material may not strictly fall into any category of mesoporous materials, they have in common that they are typically prepared from mineral constituents and have the same rigid and "stiff" character. Combined with the dramatic rise of work associated with nanostructured systems in general within chemistry, this should justify our choice. In addition, we feel that certain of these systems, such as, for example, those using organic–inorganic hybrid materials, belong more naturally within this section than that of polymer-supported organocatalysts as its contributors are often well acquainted with material science and undertake the preparations in a bottom-up type fashion more characteristic of those using mesoporous materials in general.

23.3.2
Inorganic and Inorganic–Organic Hybrid Material Supported Chiral Organocatalysts

Much like everything else within organocatalysis, the immobilization of enamine–iminium organocatalysts onto mesoporous materials quickly caught the attention of researchers after 2000. Already in 2003, the first immobilization of a proline derivative on MCM-41 was reported by a research group in India [50], but especially the thorough work of Fernández-Mayoralas and coworkers from 2005 onwards disclosed the properties of these systems in detail [51a, b]. Proline-containing organosilicon precursors containing a linker were synthesized and anchored to several mesoporous materials like MCM-41 and silica to give supported catalysts like **39** and **40** (Figure 23.7). These mesoporous catalysts were investigated extensively in organocatalytic aldol reactions of hydroxyacetone and various aldehydes. A peculiar and interesting characteristic that was revealed during these studies was the fact that the solid support actually heavily influenced the stereochemistry of the products, in fact giving isomers other than that provided by the homogeneous catalyst when using some of the aldehydes [51a, b]. These catalysts could therefore provide stereoselectivities that sometimes were complementary to those of the homogeneous catalyst. By separate experiments, the stereoselectivity changes were coupled to interactions of the reactants and solid support, possibly hydrogen bonding of certain reactants and silanol groups on the solid surface, and not due to interactions from the substitution at position 4 in the proline derivative of the immobilized catalyst. These interactions were also rather heavily influenced by the choice of solvent. Taken together with our discussion in the previous section relating to the interplay of proline catalysis and polymeric support, the diverging behavior of homogeneous (monomeric) catalyst versus immobilized catalysts, whether they be polymer or mesoporous supported, opens up entirely new possibilities for supported catalysts and offers insights that may be actively exploited in synthesis.

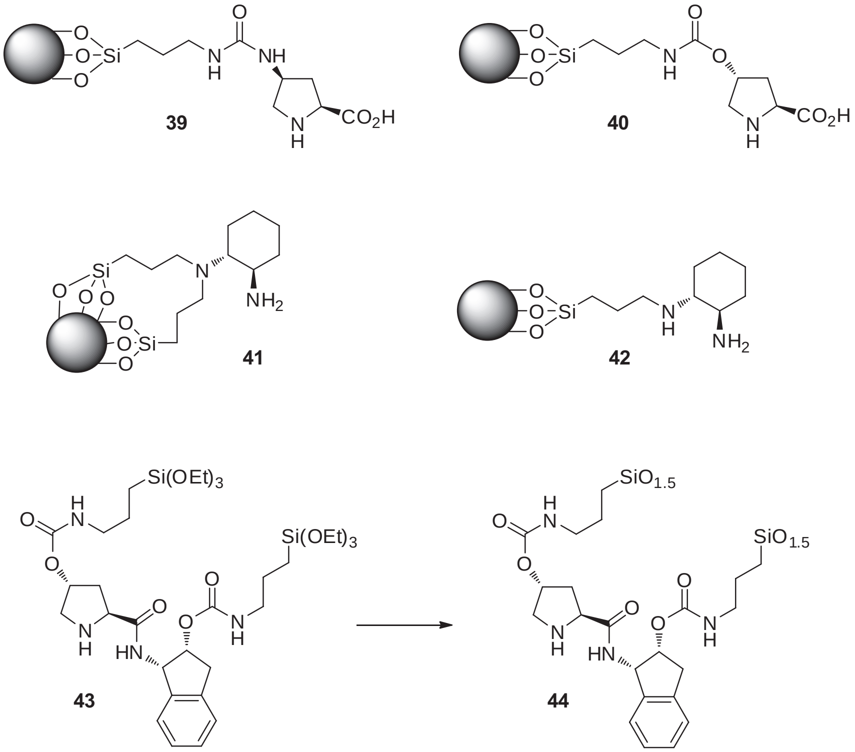


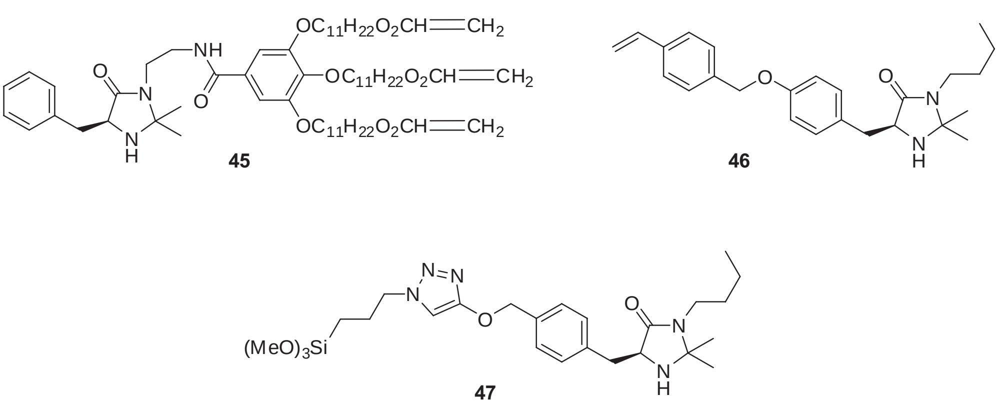
Figure 23.7 Supported enamine organocatalysts.

Magnetic nanoparticles are an attractive type of catalyst support due to the very facile separation process of catalyst and reaction mixture through the use of a simple magnet. In addition, the very small size of the particles allows for a large surface area and high catalyst loading, making them a useful alternative to mesoporous materials. The first use of magnetic nanoparticles for immobilization of a chiral organocatalyst was reported in 2008 [52]. Chiral primary amine organocatalysts were anchored to the surface of silica-covered magnetite (Fe_3O_4) nanoparticles (~8–10 nm large) to give enamine catalysts **41** and **42** (Figure 23.7). These catalysts could be dispersed in a range of solvents and were tested successfully in asymmetric aldol reactions. They could be recycled up to 11 times without significant loss of activity or selectivity.

The term silsesquioxanes is used to designate silicon structures that have the empirical formula $RSiO_{3/2}$ where R equals hydrogen or a carbon moiety. They form a sort of inorganic–organic hybrid material with structures intermediate between those of silicones and silica. Polyhedral oligomeric silsesquioxanes (POSS), one member of this group, are small caged structures that are rapidly attracting interest in nanostructured systems, particularly within material science. Very recently, the synthesis of a proline-amide bridged silsesquioxane has been reported [53]. The proline-amide organosilicon precursor **43** was polycondensated in the presence of a fluoride catalyst to give proline-amide bridged silsesquioxane **44** (Figure 23.7). The activity of the catalyst was evaluated through organocatalytic aldol reactions of benzaldehydes and cyclohexanone and compared fairly well with a homogeneous catalyst, and it could be recycled. However, compared to other proline-amides systems based on organic polymers, treated in previous sections, the activity and selectivity must be considered rather moderate. The catalyst was also tested successfully in Robinson annulations and Michael additions.

Just as for polymer-supported catalysts [9], small proline-containing peptides have been supported on mesoporous materials as well [54]. As for systems founded on organic polymers, silica-supported systems can also give high catalytic selectivity and activity, and can also be successfully recycled.

In analogy with polymer-supported catalysts, several MacMillan imidazolidinone organocatalysts supported on mesoporous structures or inorganic–organic hybrid materials have surfaced in literature. In 2005, a novel liquid crystal templated synthesis was used to prepare a nanostructured imidazolidinone catalyst [55]. Imidazolidinone precursor **45** (Figure 23.8) formed a liquid crystalline phase in acidified water and was subsequently radically photo-crosslinked with retention of microstructure using a photo-initiator. The catalysts were tested successfully in organocatalytic Diels–Alder reactions. In 2006, a research group in Singapore reported imidazolidinones immobilized on siliceous and polymer-coated mesocellular foams [56]. Either organosilicon-modified imidazolidinone precursors were anchored by traditional silicon chemistry or the surface of the mesocellular foams was capped by silylation and covered with a polymer layer by copolymerization of functional styrenic derivative **46** (Figure 23.8) and divinylbenzene under suitable conditions. The catalysts were tested in asymmetric Diels–Alder cycloadditions and Friedel–Craft alkylations. In 2011, hollow-structured, phenylene-bridged periodic mesoporous organosilica spheres (using uniform α-Fe_2O_3 nanoparticles as hard template) were functionalized by MacMillan catalyst precursors such as **47**


$OC_{11}H_{22}O_2CH{=}CH_2$
NH
O
N
$OC_{11}H_{22}O_2CH{=}CH_2$
O
$OC_{11}H_{22}O_2CH{=}CH_2$
N
H
45
O
O
N
N
H
46
N=N
N
O
O
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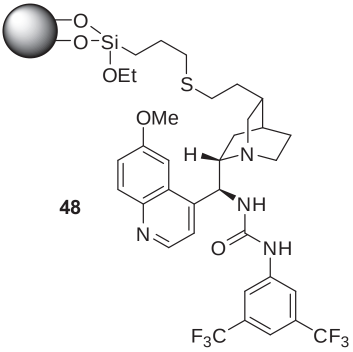
(MeO)$_3$Si
N
H
47

Figure 23.8 Precursors for supported MacMillan imidazolidinone organocatalysts.

48



49

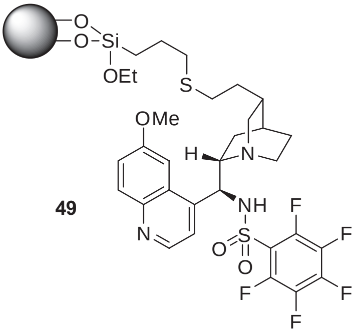


Figure 23.9 Magnetite-supported cinchona organocatalysts.

(Figure 23.8) by a grafting procedure [57]. These catalysts were tested in asymmetric Diels–Alder reactions, and they were recycled up to seven times with little loss of selectivity, but with diminishing activity, apparently because of damage inflicted upon the mesoporous structure during reuse [57].

Very recently, Connon and coworkers in Ireland published a thorough study on the immobilization of several chiral organocatalysts onto magnetic nanoparticles [58]. Included in this work was also magnetite-supported cinchona derivatives **48** and **49** (Figure 23.9). The chiral urea catalyst **48** exhibited a clearly reduced catalytic activity compared to the homogeneous catalyst in asymmetric Michael addition reactions. It also performed poorly when reused more than a few times. Such an "aging" effect had also been observed by Takemoto and coworkers in 2006 when using a homogeneous PEG-linked chiral thiourea catalyst [59]. On the other hand, other researchers have reported improved activity and selectivity for thiourea cinchona catalysts compared to homogeneous system when supported on mesoporous silica and tested in asymmetric Friedel–Crafts reactions [60]. In fact, referring to the study of Connon and coworkers, it was discovered that the nanoparticles themselves, used to prepare anchored urea **48**, were actually catalytically active and gave rise to background catalysis, undermining overall selectivity [58], a powerful manifestation of the heightened activity of many particles when going down to the nanomolecular scale.

Magnetite-supported cinchona sulfonamide catalyst **49**, unlike urea catalyst **48**, exhibited excellent reusability in desymmetrization reactions, being almost unaffected after 20 reaction cycles. However, the product selectivity was consistently lower than for the corresponding homogeneous catalyst, and background catalysis by the nanoparticles themselves was again shown to be the likely cause [58]. As for influential immobilization methodology, one can easily recognize the classic immobilization of cinchona derivatives **48** and **49** by linkage via the olefin bridge of the cinchona alkaloids using the thiol-ene coupling, a methodology that, as we have seen, has survived successfully from its development decades ago all the way up to present, a powerful example of how a clever and generic immobilization methodology can influence and motivate research over decades even as the supported catalysts or reagents themselves, or their countless applications, have changed beyond all recognition.

23.4
Conclusions and Outlook

In this chapter, we have reviewed various supported chiral organocatalysts and have focused our attention on covalently anchored catalysts of the most important types, inevitably leaving out credible work that should have been included. As we have repeatedly emphasized [7, 9], we believe simple cost-issues to be the single most prevailing obstacle to more widespread utilization of supported catalysts, preserving the current and limited status quo, and think research efforts could more favorably be directed accordingly. As such, useful generic methodology that can be used to prepare a broad range of supported organocatalysts, or other catalysts for that matter, should be a self-evident and obvious priority for all researchers taking part in the development of the field. The apparent and increasing willingness and inclination of scientists to engage in interdisciplinary research efforts and scientific collaborations, manifested by the advent of numerous bottom-up type approaches to materials as varied as organic polymers, mesoporous inorganic solids, inorganic–organic hybrid materials, and nanoparticles alike, certainly promise well for the future and are mutually beneficial for all taking part in it. In time, the educational systems will also almost certainly change accordingly, removing entrenched, but sometimes “invisible,” barriers existing between disparate fields of chemistry and increasing receptiveness to new methodology.

As a final comment, it does ever more seem to be the case that the applicability of an immobilization strategy must be ascertained on a case-by-case basis and that no truly general strategies can be adopted. The traditional view of a solid support as an “inert scaffold” has been increasingly shown to be seriously mistaken, especially when taking into consideration the work conducted on polymer-supported enamine–iminium organocatalysis in aqueous environments over the last half-decade and the previous work on nanoparticle-supported organocatalysts. However, this is not meant to be construed in such a way to mean that widely applicable strategies cannot be developed – the legacy of the approximately 50 years of rich experience with supported substrates, reagents, and catalysts already behind us suggests otherwise.

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24
Water in Organocatalytic Reactions

Francesco Giacalone and Michelangelo Gruttadauria

24.1
Introduction

Water is a green solvent: it is cheap, safe and environmentally friendly compared with organic solvents. Pfizer Corp. has defined a solvent guide that encourages the use of preferred solvents, for example, water or ethyl acetate, over usable solvents, for example, dimethyl sulfoxide (DMSO), and undesirable solvents, for example, dimethylformamide (DMF) [1]. However, chemical reactions carried out in or on water are not necessarily green reactions. Indeed, if we consider a reaction involving two species (A and B) and a product (C), the requirement for an ideal situation is when the product C has zero solubility and is quantitatively recovered by filtration, leaving no starting compounds A and B. In this case pure water can be recovered. This is, of course, an ideal case and in reality the filtrate will contain A, B, and C. In this case, the greenness and economic benefit of the process will depend on the kind of process needed to obtain pure water without traces of organic molecules and, if employed, any kind of metal-based catalyst or organocatalyst.

Nevertheless, water is increasingly used as an additive or alternative solvent in many organic transformations [2]. From a practical and synthetic standpoint, the benefits of using water can arise from the avoidance of dry solvent substrates and laboratory glassware.

The use of water as additive or reaction medium has also attracted much attention in the field of asymmetric organocatalytic reactions [3], although its use in organocatalytic processes has been questioned [4]. Two questions have been exposed: one about the greenness and the other about the efficiency of an organocatalytic reaction carried out under aqueous conditions. The combined use of the words “aqueous” and “organocatalytic” does not necessarily mean an environmental and economical process; however, in this chapter we will show that an organocatalytic reaction carried out in an aqueous medium can be a very efficient process. At the end of the twentieth century the first organocatalytic intermolecular direct aldol reaction was reported [5]. The catalyst, proline, acts as a class I aldolase-mimic activating substrates through an iminium ion formation step followed by

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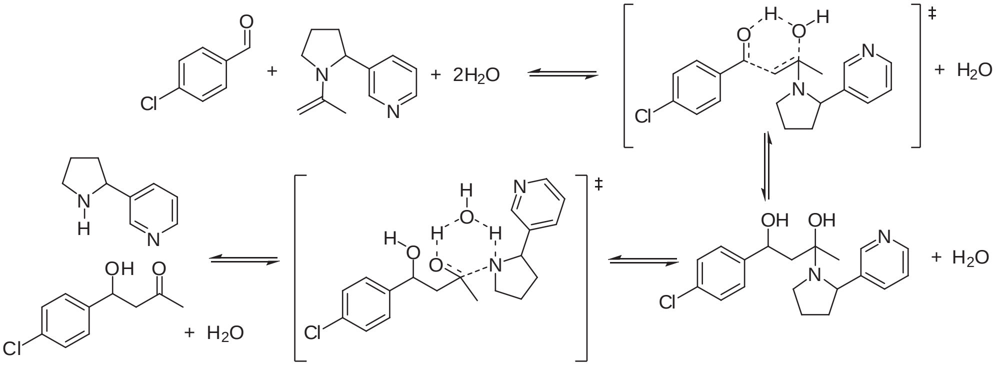
enamine formation [6]. Since then, many studies have been carried out on organocatalytic asymmetric aldol reactions and, for this reason, this introduction is mainly focused on this topic.

In general, organocatalytic aldol reactions are carried out in a one-pot operation by stirring a donor carbonyl compound and an acceptor electrophile in the presence of an amine-based catalyst in conventional organic solvents such as DMSO, DMF, or $CHCl_3$, which should be avoided because they are toxic, flammable, and volatile. In the catalytic enamine cycle water is formed; however, its removal is not required for the formation of enamine intermediates, which proceed to react directly with an electrophile. This water tolerance is a desirable characteristic of an organocatalyst and has prompted many researchers to investigate its role in determining the activity and stereoselectivity of organocatalysts. However, in principle, water may interfere with the transition state formed between organocatalyst and substrate molecules. This could disrupt the hydrogen bonds and other polar interactions, thus reducing the catalytic activity and stereocontrol.

Organocatalytic reactions have been investigated using water in small (1–3 equiv.) or higher amounts. It was reported that the proline-catalyzed reaction of acetone and 4-nitrobenzaldehyde tolerated a small amount of water (<4 vol.%) without affecting the enantiomeric excess of the aldol product. However, increasing the amount of water (20 vol.%) severely compromised the enantioselectivity and decreased the rate of formation of the aldol product [5b].

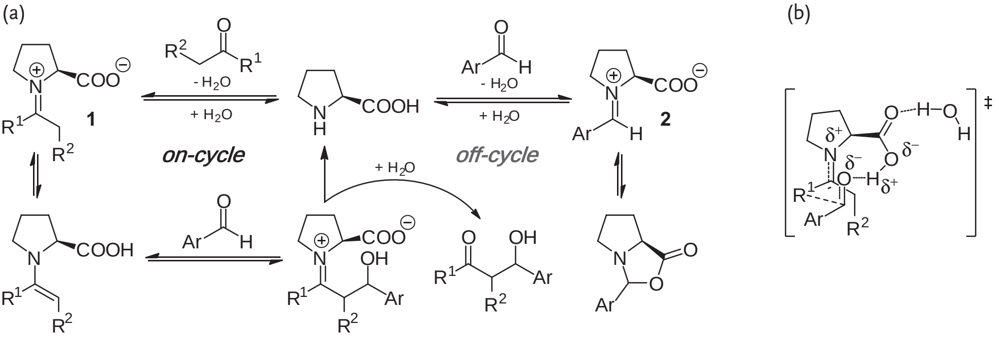
Janda *et al.* described the aldol reaction between acetone and 4-chlorobenzaldehyde catalyzed by nornicotine in water. Although the aldol product was isolated in low enantiomeric excess (20%) it was the first experiment showing the catalytic role of water in an organocatalytic reaction. The authors proposed that in the first step of the reaction one molecule of water completes a six-membered transition state in which the C–C bond formation, proton transfer from water to aldehyde, and C–OH bond formation occur simultaneously to give a β-hydroxy-hemiaminal species. In the second step, a second molecule of water promotes cleavage of the C–N bond via proton donation, while it regenerates itself by accepting a proton from the OH group (Scheme 24.1) [7].



Scheme 24.1 Proposed mechanism for nornicotine-catalyzed aqueous aldol reaction.

A small amount of water has had a role in other organocatalytic reactions. The presence of 1 equiv. of water improved the yields while maintaining excellent stereoselectivity in the reaction between thiopyranone and aldehydes in DMF [8]. The presence of water allowed the use of a smaller excess of the donor ketone and increased the yield of the aldol products when cyclic ketones were employed [9]. Rate acceleration in the proline-catalyzed aldol reaction without negative effect, or even with a positive effect, on stereoselectivity was observed when water was used at up to 500 mol% in DMF solution [10].

What is the role of water under these conditions? It has been suggested that water suppresses the formation of proline-oxazolidinone, which has been considered to be a parasitic species [11]. Then, the role of water is to prevent deactivation rather than to promote activity. Studies, carried out on the proline-catalyzed reaction between acetone and 2-chlorobenzaldehyde allow one to hypothesize a conflicting role of water. Water increases the total catalyst concentration due to suppression of unproductive species and decreases the relative concentration of productive intermediates by shifting the iminium ion back to proline [12]. Addition of water suppresses formation of both on- and off-cycle iminium ions **1** and **2** by Le Châtelier's principle (Scheme 24.2a). The net effect of added water on the globally observed rate will depend on the relative concentrations of iminium ions **1** and **2**, which may be different for different aldehydes and can be a function of substrate concentrations and rate and equilibrium constants. Seebach and Eschenmoser have raised doubts about the fact that oxazolidinones are unproductive and parasitic species in proline-catalyzed aldol reactions [13]. The small excess of water will potentially facilitate proton-transfer in the transition state (Scheme 24.2b), which both lowers the LUMO of the incoming electrophile as well as directs the enantioselectivity of the newly formed stereocenters.



Scheme 24.2 (a) Proposed catalytic cycle for aldol reaction; (b) transition state for proline-catalyzed aldol reaction.

What about the use of water in higher amounts? Although water does not dissolve organic reagents, it still accelerates the rate of many reactions [14]. Water molecules bring the organic reagents close to each other, then the reaction can take place in a concentrated organic phase away from water molecules.

However, unlike native aldolases or aldolase antibodies, in the presence of bulk water the aldolase-type organocatalytic aldol reaction catalyzed by simple amino acids does not take place or takes place with low enantioselectivity [5b,15]. Simple amino acids, such as proline and valine, catalyzed the neogenesis of carbohydrates under prebiotic conditions using glycol aldehyde as the substrate. Although the corresponding carbohydrates were isolated in low ee values, the transfer of their chiral information to tetroses and hexoses [16], which are the building blocks of prebiotic RNA and most common polysaccharides, could explain the development of homochirality on the early Earth [17]. Actually, enzyme aldolases form a hydrophobic pocket at their active site that diminishes contacts between bulk water and the reaction transition states; thus, an enzyme-catalyzed reaction might be regarded as taking place in organic solvent wherein the enzyme itself is essentially a water-soluble molecule that plays its catalytic role thanks to the stereodefined array of amino acid side-chains. Small organocatalysts, such as proline, cannot form this hydrophobic pocket and, therefore, organocatalytic reactions with aqueous solvents result in poor yield and stereoselectivity.

Before starting a more detailed discussion on the use of water in asymmetric organocatalytic reactions, we should explain further about how to consider these reactions when water is used as reaction medium. Three kinds of reactions can be designed, namely, “on water,” “in water,” and “in the presence of water” reactions. Sharpless has defined “on water” reactions as a group of organic reactions that take place as an emulsion and that exhibit reaction rate acceleration compared to the same reaction in an organic solvent [18]. Hayashi has discussed the use of “in water” or “in the presence of water” terminology [19]. He proposed the use of “in water” when the reactants participating in the reaction are homogeneously dissolved whereas “in the presence of water” should be used for a reaction that proceeds in a concentrated organic phase with water being present as a second phase that influences the reaction in the organic phase. The main difference between “on water” and “in the presence of water” reactions lies in the observed effect: for “on water” reactions this is rate acceleration, whereas for “in the presence of water” reactions this is an increased enantioselectivity. The enhanced activity of organic catalysis “on water” has been investigated theoretically [20]. Free OH groups of interfacial water molecules play a key role in catalyzing reactions via the formation of hydrogen bonds. Indeed, calculations showed that approximately one in every four interfacial water molecules has a dangling OH group that protrudes into the organic phase; catalysis is, then, expected when these OH’s form stronger hydrogen bonds with the transition state than with the reactants.

However, since the main goal of this chapter is to discuss enantioselective organocatalytic reactions, attention will be focused on reactions carried out “in the presence of water.” Although the exact role of water is not clear, water is essential for high stereoselectivity. In general, these reactions take place in emulsion in the presence of an organocatalyst bearing an appropriate hydrophobic moiety. Data reported in the literature suggest that organocatalytic molecules could be organized at the organic phase/water interface and that their organization depends on the nature of the hydrophobic moiety group and on the catalyst-to-water ratio. A

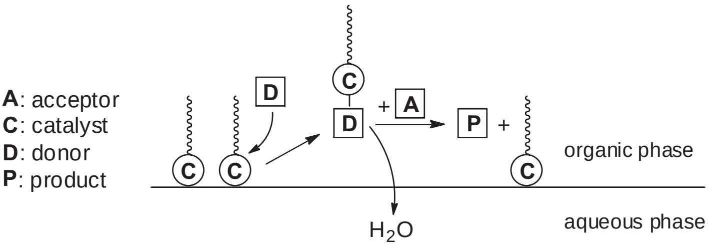


Figure 24.1 Schematic representation of emulsion catalysis.

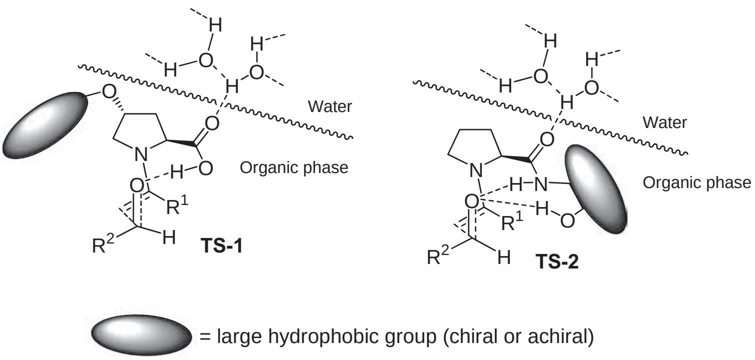
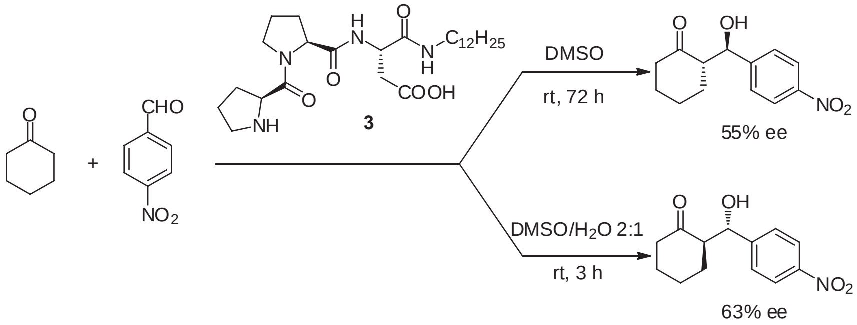


Figure 24.2 Proposed transition states for 4-substituted proline and prolinamide-catalyzed aldol reaction in water.

tentative mechanism is described as follows (Figure 24.1): the organic donor molecule D reacts with catalyst C at the interface to give the enamine intermediate with elimination of a molecule of water that is excluded from the organic phase, driving the equilibrium towards enamine formation. The enamine intermediate is more hydrophobic than catalyst C, therefore the enamine intermediate moves into the organic phase. Thus, carbon–carbon bond formation between the enamine intermediate and the acceptor A occurs rapidly in the highly concentrated organic micellar phase through a transition state similar to that observed in organic solvents and then hydrolysis of the enamine intermediate proceeds. In other cases, the organocatalyst may contain both hydrophobic and hydrophilic domains – then the carbon–carbon bond formation could take place at the interface.

Hydroxy groups of the surface water molecules suspended at the hydrophobic interface might form hydrogen bonds with the carbonyl oxygen atom as in TS-1 or the amide oxygen atom as in TS-2, but not with the NH and OH groups of the catalyst (TS-2) as they are surrounded by hydrophobic groups (Figure 24.2). In the latter case, the reaction proceeds via transition state TS-2 by forming an additional hydrogen bond, thus making amidic NH more acidic, leading to a compact transition state. Such compact networks may ensure high enantioselectivity.

Water may play other roles; for instance, in the conformational switch from one turn conformation to another with the opposite twist in the peptide catalyst **3**, causing a reversal in enantioselectivity upon addition of water (up to 50%) to DMSO (Scheme 24.3) [21]. Such a switch of enantioselectivity of a given catalyst by changes of solvent is unusual, but a few reports have been described [22].



Scheme 24.3 Aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalyzed by tripeptide **3**.

As discussed before, we will report examples in which water both increases activity and stereoselectivity of the organocatalyst, when used from a substoichiometric amount to a very large excess (reaction medium). Whether these reactions are carried out with a catalytic amount of water or in truly aqueous medium, the most important aspect was that water increased the efficiency and stereoselectivity of the catalyst and this is, in our opinion, extremely interesting from a synthetic point of view. On the other hand, a deeper understanding of the role of water, whatever the amount employed, can help in the design of more active and selective organocatalysts.

24.2
Aldol Reactions

24.2.1
Primary Amines

The deployment of natural primary amino acids as organocatalysts for the asymmetric aldol reaction, albeit useful because of the easy availability of such molecules, is not an interesting synthetic approach due to the low enantioselectivities observed, long reaction times, and high catalytic loadings needed [23]. For instance, L-alanine was able to catalyze the aldol reaction in excellent stereoselectivity, but with long reaction times, when employed in aqueous (10 equiv.) DMSO. The addition of water was crucial for the success of the reaction. The more hydrophobic

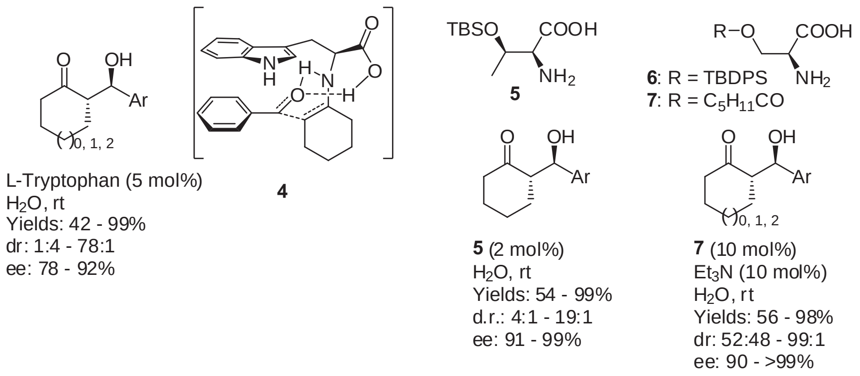
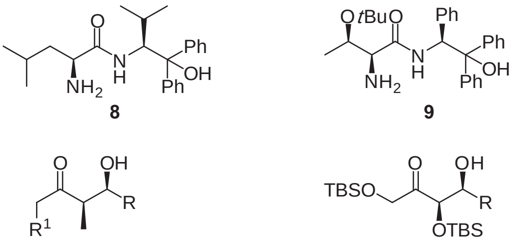


Figure 24.3 Proposed transition-state for L-tryptophan catalyzed aldol reaction and structure of catalysts **5–7**.

L-tryptophan gave good results when it was used in water (Figure 24.3). To explain the stereochemical outcome, the authors proposed a model for the transition state in which the enamine attacks the aldehyde from the *Re* face and the aromatic side chain of tryptophan facilitates the formation of a hydrophobic core with other hydrophobic substrates in water (**4**, Figure 24.3) [23b].

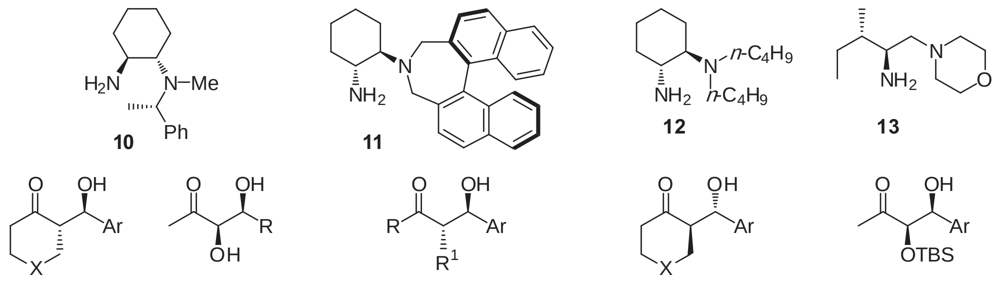
The hydrophobicity of primary amino acids can be enhanced by modification of their structure with the proper hydrophobic group. A simple approach, which follows Hayashi's idea of derivatizing the OH group of hydroxyproline with hydrophobic silyl groups (see below), is the use of silyloxy derivatives of L-serine and L-threonine. In particular, *tert*-butyldimethylsilyl-protected L-threonine **5** was found to be an active and selective catalyst (Figure 24.3) [24]. This catalyst gave *anti*-aldol products with cyclic ketones and *syn*-aldol products with acyclic ketones (such as protected hydroxyacetone) on reaction with aromatic aldehydes, with high ee and de. The limitation associated with catalyst **5** is that it does not work well with aliphatic aldehydes. Good results were also obtained using *tert*-butyldiphenylsilyl -protected L-serine **6**. Unprotected L-serine was inactive in water [25]. In contrast *O*-acylation of L-serine gave an active catalyst under aqueous conditions. Catalyst **7** (10 mol%) was employed in the presence of triethylamine as additive (Figure 24.3). The latter molecule was also recovered and reused [26]. The ability to recover and recycle expensive organocatalysts or organocatalysts used in high amounts from the reaction mixture after completion of the reaction is highly desirable. Indeed, recyclable asymmetric organocatalysts are molecules of great interest [27].

The hydrophobicity can also be enhanced by modification of the amino acid into an amide catalyst bearing a *gem*-diphenyl group, an approach previously developed by Singh *et al.* [28] Amide **8** [29], with 4-nitrobenzoic acid as additive, and amide **9** [30] were employed in brine (Figure 24.4). The reaction failed when the hydrophilic dihydroxyacetone was used. In contrast, the use of more hydrophobic ketones, such as TBS-protected dihydroxyacetone, was successful. However, the enantioselectivity of the reaction (with catalyst **9**) decreases with increasing length of the



8 (20 mol%)	**9** (15 mol%)
4-NO$_2$C$_6$H$_4$COOH (20 mol%)	Brine, rt
Brine, rt	Yields: 55 - >99%
Yields: 78 - 98%	dr: 3:1 - 11:1
dr: 3:1 - 7:1	ee: 87 - 98%
ee: 73 - 97%	

Figure 24.4 Structure of catalysts **8** and **9** and their catalytic activity.



10 (10 mol%)	**10** (10 mol%)	**11** (3.5 mol%)	**12** (5 mol%)	**13** (10 mol%)
TFA (10 mol%)	TFA (10 mol%)	TfOH (3.5 mol%)	TfOH (5 mol%)	TCA (10 mol%)
H$_2$O, rt	DMF/H$_2$O 9:1, rt	H$_2$O, rt	H$_2$O, rt	H$_2$O, rt
Yields: 76 - 90%	Yields: 79 -89%	Yields: 23 - 96%	Yields: 34 - 99%	Yields: 65 - 94%
dr: 86:14 - 99:1	dr: 95:5 - 98:2	dr: 80:20 - 99:1	dr: 79:21 - 99:1	dr: 68:32 - 93:7
ee: 90 - >99%	ee: 91 - >99%	ee: 86 - 98%	ee: 84 - 98%	ee: 83 - 97%

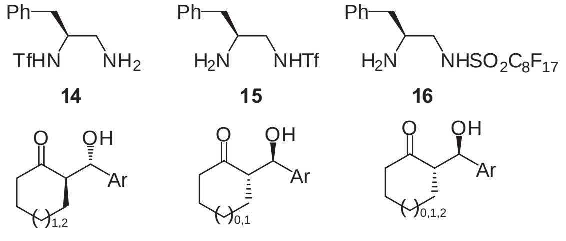
Figure 24.5 Structure of catalysts **10–13** and their catalytic activity.

aliphatic ketone. Thus, the right balance between several factors must be taken into account for the best stereochemical outcome of the reaction. These factors are not well understood, so far.

The hydrophobic *gem*-diphenyl group in amides **8** and **9** contains an additional stereocenter, which also plays a role in enantiomeric differentiation. Following a similar approach, the primary–tertiary amine **10** (Figure 24.5) containing a chiral hydrophobic substituent at the tertiary nitrogen atom was developed [31]. In this case a strong Brønsted acid such as trifluoroacetic acid (TFA) is essential to obtain *anti*-aldol products with high enantioselectivity and diastereoselectivity. Hydroxyacetone was also used as a donor in the reaction with several arylaldehydes or cyclohexyl-aldehyde. In these cases, the use of a mixed solvent system (i.e., DMF/water 10vol.%) provides an ideal environment because the balanced solubility of both hydrophobic aldehydes and hydrophilic hydroxyacetone gives higher enantioselectivities than those obtained in pure water.

An even bigger chiral hydrophobic moiety is present in catalyst **11** (Figure 24.5) [32]. This catalyst efficiently catalyzed the asymmetric aldol reaction of aryl aldehydes with cyclic ketones in water with high diastereoselectivities and enantioselectivities. The reaction was carried out in the presence of 3.5 mol% of triflic acid (TfOH) as acid additive. Appropriate choice of the hydrophobic moiety may avoid the presence of additional chiral centers in the catalyst. Thus, a primary–tertiary amines bearing two *n*-butyl groups (**12**, Figure 24.5) [33] or a morpholine group (**13**, Figure 24.5) [34] were found to be good catalysts for the aldol reaction between cyclic ketones or TBS-protected hydroxyacetone and substituted benzaldehydes in the presence of water. In both cases an acid additive was needed, such as TfOH or trichloroacetic acid (TCA).

In the above examples catalysts were employed in the absence of additive or in the presence of a weak acid (4-nitrobenzoic acid) or a strong acid (TCA, TFA, or TfOH). When acid protons, such as carboxylic protons of amino acids, are available no acid additives are needed. In other cases, in which no acid protons are present (e.g., prolinamide derivatives), the combination of a highly hydrophobic catalyst and the presence of water may avoid the use of acid additives. In these cases, the positive effect of water could also be ascribed to the fact that it may reinforce the acidity of the amide NH bond, because of the hydrogen bond formed between a free hydroxy group of surface water molecules at the hydrophobic interface and the amide oxygen atom of the organocatalyst (Figure 24.2). Acid additives were usually added when no acid protons are present in the catalyst structure, such as in primary–tertiary amines. In these cases, protonation of the tertiary amine nitrogen atom furnishes the hydrogen atom able to coordinate the carbonyl oxygen atom of the acceptor. Further examples of primary amine catalysts are reported in Figure 24.6. Catalysts **14** [35] and **15** [36] were used in brine at room temperature and 0 °C, respectively. Long reaction times were required and low ee values were



14 **15** **16**

14 (20 mol%)	**15** (10 mol%)	**16** (10 mol%)
TFA (5 mol%)	TFA (5 mol%)	TFA (5 mol%)
brine, rt	brine, 0 °C	brine, rt
Yields: 12 - 81%	Yields: 12 - 93%	Yields: 47 - 96%
dr: 56:44 - 96:4	dr: 71:29 - >99:1	dr: 50:50 - >99:1
ee: 79 - 96%	ee: 85 - 93%	ee: 25 - 96%

Figure 24.6 Structure of catalysts **14–16** and their catalytic activity.

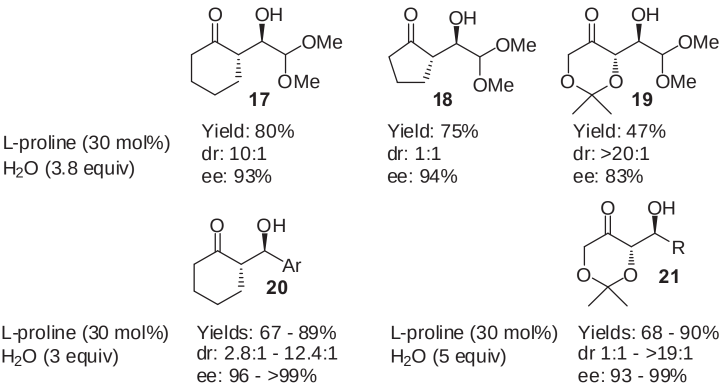


Figure 24.7 Structure of aldols **17–21**.

obtained using acetone. Compound **16** was modified with a longer fluorous alkyl chain to increase hydrophobicity and to allow its recovery by solid-phase extraction using fluorous silica gel [37].

24.2.2
Secondary Amines

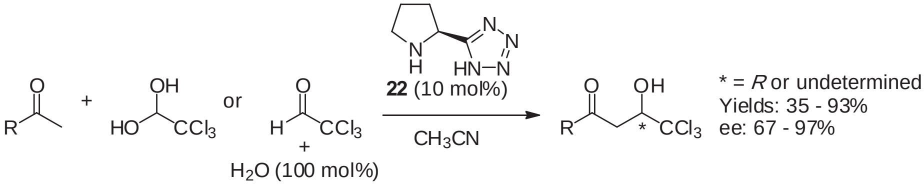
The most famous secondary amine employed in organocatalysis is proline. In addition to the examples reported in the introduction regarding the use of proline under aqueous conditions, it is worth further describing other applications of proline under the same conditions. No enantioselectivity was observed in proline-catalyzed aldol reactions in phosphate buffer [38] and aqueous micelles [39]. When proline was used with camphorsulfonic acid as co-catalyst good yields and stereoselectivities were obtained using a 4 : 1 (v/v) ketone : water ratio [40].

Although several groups found that simple proline is not a useful catalyst under aqueous conditions, under specific, wet, conditions simple proline is able to catalyze aldehyde–aldehyde and aldehyde–ketone aldol reactions enantioselectively (aldols **17–20**, Figure 24.7). Wet conditions required the use of 30 mol% of proline and 3–3.8 equivalents of water [41].

The use of proline (30 mol%) as catalyst in the reaction between dimethyl-1,3-dioxan-5-one and 4-nitrobenzaldehyde in DMSO gave the aldol product in low yield and stereoselectivity. Improved performances were displayed when 5 equivalents of water were used, furnishing aldol products in high yields and stereoselectivities with a set of aldehydes (aldols **21**, Figure 24.7) [42].

Interesting results were obtained with proline-tetrazole **22** in the reaction between ketones and chloral monohydrate or anhydrous chloral and water (100 mol%). High yields and stereoselectivities were observed (Scheme 24.4). Addition of a higher amount of water increased the enantioselectivity of the reaction and decreased the diastereoselectivity. In contrast, the use of a catalytic amount of water (20 or 50 mol%) disabled the catalytic cycle (ca. 5% conversion).

The authors hypothesized that water could prevent the formation of the iminium ion from catalyst and chloral [43].



Scheme 24.4 Proline-tetrazole catalyzed aldol reactions.

As shown by the above results, reactions catalyzed by proline require the use of a large amount of such a catalyst and the reaction conditions must be finely tuned. These findings have led several authors to develop a number of proline derivatives of type I, II, and III (Figure 24.8). The increased hydrophobicity of these molecules allowed their use in the presence of water with increased activity and stereoselectivity.

24.2.3
Prolines Substituted at the 4-Position

Starting from the easily available 4-hydroxyproline, several substituted prolines have been synthesized and successfully used as catalysts in the aldol reaction in the presence of water. The first 4-substituted hydroxyproline prepared was compound **23** bearing a TBDPS group (Figure 24.9) [15]. This catalyst was thoroughly investigated by studying the effect of the amount of water and the effect of the amount of catalyst. Catalyst **23** can be employed in 1 mol% by using 2 equivalents of ketone, reaching a high level of enantio- and diastereoselectivity. The same catalyst has also been employed in the construction of quaternary carbon centers through cross-aldol reactions between ketones and β,γ-unsaturated keto-esters in water (Figure 24.9). Screening of solvents (DMF, $CHCl_3$, toluene, *i*-PrOH, EtOH, MeOH) evidenced that in toluene the reaction occurred with high stereoselectivity while protic solvents gave a faster reaction. The use of water also gave a faster reaction and higher yields and stereoselectivities were obtained [44].

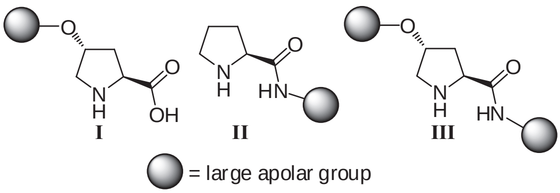


Figure 24.8 General structure of proline derivatives.

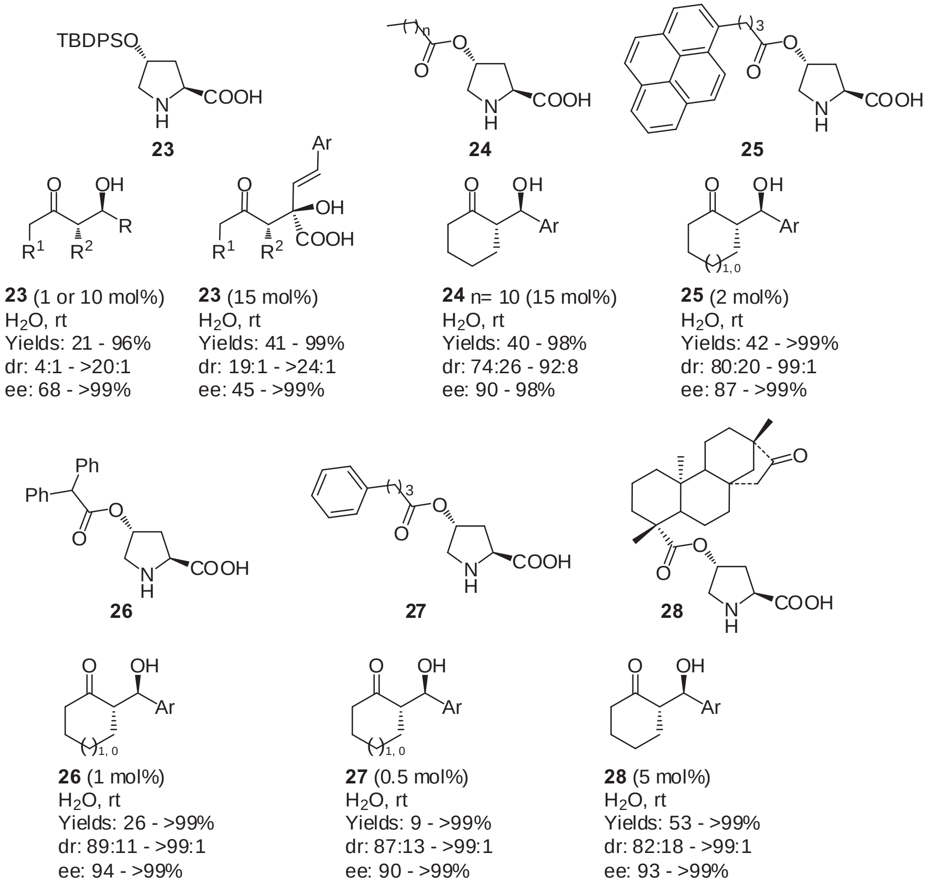
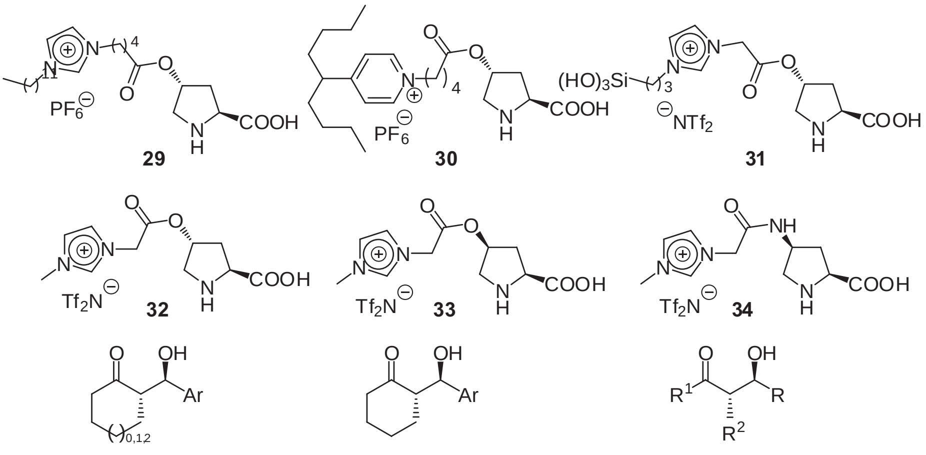


Figure 24.9 Structure of catalysts **23–28** and their catalytic activity.

These results paved the way to the discovery of new 4-substituted prolines. Several 4-acyloxyprolines **24** (Figure 24.9) were also screened in the reaction between cyclohexanone and benzaldehyde. The length of the acyl side chain affected the yield, with the best results being obtained when the hexanoyloxy (**24**, $n = 4$) moiety was employed [15]. A water/oil (W/O) emulsion was formed by addition of a specific amount of water to cyclohexanone containing catalyst **24** ($n = 10$) under vigorous stirring [45]. Dynamic light-scattering showed that the sizes of the spherical emulsion droplets formed from **24** ($n = 10$) were about 0.1–0.2 μm. A metastable O/W emulsion can also be obtained when the ratio of the catalyst to cyclohexanone is optimized. The two types of emulsions (W/O and O/W) formed from **24** ($n = 10$) resulted in an aldol product with the nearly same yield and stereoselectivity, indicating that the aldol reaction can occur efficiently in emulsion even if with an excess of water. Catalyst **24** ($n = 10$) was used in 15 mol% in a W/O emulsion to give aldol products with high stereoselectivities. By using the appropriate acyl chain, the activity of the catalyst can be finely tuned, allowing its use in much lower loading while maintaining a high level of stereoselectivity in the final aldol products. Proline possessing a highly hydrophobic 4-(pyren-1-yl) butanoyloxy group (**25**, Figure 24.9) was used in only 2 mol% at room temperature without additives to give aldol products in excellent stereoselectivities [46]. Moreover, the activity of 4-acyloxyprolines was improved when 2,2-diphenylacetoxy and 4-phenylbutanoyloxy groups were installed in the proline structure. Catalyst **26** was used in 1 mol% loading whereas catalyst **27** was used in only 0.5 mol%. Catalysts **26** and **27** afforded aldol products with high to excellent enantio- and diastereoselectivities, even when cyclopentanone was employed (Figure 24.9) [47]. It is important to stress that simple catalysts such as **23** or **27** do not need the use of low temperatures or additives and do not need new chiral centers in addition to those of inexpensive *trans*-4-hydroxy-L-proline. Moreover, acyloxyprolines, such as **27**, can be very easily prepared in one step by direct O-acylation starting from very inexpensive carboxylic acids [48]. 4-Hydroxyproline bearing the lipophilic isosteviol skeleton (**28**, Figure 24.9) was also prepared by the one-pot procedure and used in higher catalytic loading (5 mol%) in the reaction between arylaldehydes and cyclohexanone. The use of hydrophilic acetone as donor resulted in a low yield when the reaction was carried out in the presence of water [49].

4-Acyloxyprolines can also be modified with ionic liquid-tags. The use of the proper ionic liquid-tag enables the use of these catalysts in the presence of water and their recovery and reuse. Indeed, the solubility of ionic liquid-anchored organocatalysts can be tuned by an accurate choice of cations and anions groups present in their structure, and the solubility of ionic liquids can be readily tuned with different cations and anions. This approach allows phase separation to be realized from organic as well as aqueous media. Following the proper extraction procedure, it could be possible to separate the catalytic molecule from the product and to allow its reuse.

Since the use of water as reaction medium allows, in many cases, the obtainment of products with higher optical purity it might be expected that more hydrophobic structural analogs of catalysts **24** would possess a much higher activity and stereoselectivity when used in water. To test this hypothesis new ionic liquid-anchored proline derivatives were prepared (**29** and **30**, Figure 24.10) bearing long-chain hydrocarbon groups at the imidazolium nitrogen atom or in the 4-position of the pyridinium moiety [50]. However, these catalysts were employed in high catalytic amount (15–30 mol%) compared to the simpler acyloxyproline bearing no ionic liquid-tags (**25–27**). Replacement of the hydrophobic anion of catalysts **29** and **30** (NTf_2) with hydrophilic anions, such as BF_4 or Cl, furnished molecules completely soluble in water. These molecules did not catalyze the aldol reaction. On the other hand, a good balance between hydrophilic and hydrophobic sections in the structure of an organocatalyst may enhance its catalytic activity and enable a better recovery. For this purpose catalyst **31**(Figure 24.10) was prepared and it then used (10 mol%) in water to give aldol products in good yields and high to excellent stereoselectivity [51]. The role of water was evident when catalyst **32** was used under heterogeneous conditions in water instead of homogeneous



32 (5 mol%)
H_2O, rt
Yields: 25 - 98%
dr: 58:42 - 98:2
ee: 80 - 99%

33 (0.1 - 10 mol%)
H_2O, rt
Yields: 44 - >99%
dr: 80:20 - >99:1
ee: 70 - >99%

34 (0.1 - 10 mol%)
H_2O (1.2 equiv), rt
Yields: 35 - >99%
dr: 56:44 - >99:1
ee: 35 - >99%

Figure 24.10 Structure of catalysts **29–34** and their catalytic activity.

conditions in [Bmim][Tf_2N]. In water both enantio and diastereoselectivities increased significantly (ee increase up to 19%) [52]. In the presence of a small amount of water (ca. 4 vol.%) aliphatic aldehydes (*iso*-butyraldehyde and cyclohexanecarboxaldehyde) also afforded the corresponding aldol products in good yields and excellent stereoselectivities.

The possibility of having an organocatalyst that could work in lower catalytic amount prompted a search for new structures and new reaction conditions other than those previously reported. Ionic liquid-anchored proline **33** (Figure 24.10) having a 1,4-*cis*-configuration, unlike compound **32**, which has a 1,4-*trans*-configuration, was a powerful catalyst for the aldol reaction [53]. Again, water was found to be a much better reaction medium. *cis*-Catalyst **33** was synthesized considering that the ionic tag and its Tf_2N-counterion are in spatial proximity to the reactive centers during the rate-determining enamine addition step. If an internal electrostatic stabilization of the transition state was active, a reaction rate enhancement should be observed. The authors referred to this hypothesis as a "*cis* effect." Catalyst **33** was then used in the aldol reaction with several aromatic aldehydes (0.1–2 mol%) and with aliphatic aldehydes (10 mol%) with excellent results. A more robust amide linkage is present in catalyst **34** (Figure 24.10). This catalyst was also employed in the range 0.1–10 mol% with excellent results in the presence of 1.2 equiv of water. The use of larger amount of water (12 equiv. or large excess) had deleterious effects on conversion and enantiocontrol [54].

Quantum mechanical calculations have predicted the transition state geometries for the reaction of cyclohexanone enamine with benzaldehyde [55]. Transition states involving the *Re* attack on the *anti*-enamine are lower in energy than the

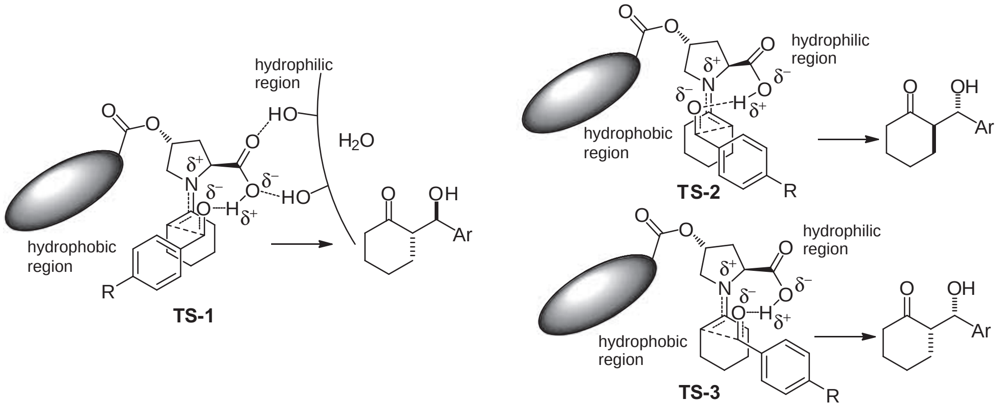


Figure 24.11 Proposed transition states of the aldol reaction between cyclohexanone and arylaldehydes.

transition states for *Si* attack on the *syn*-enamine. To explain the observed enhanced stereoselectivities it could be hypothesized that transition state TS-1 (Figure 24.11) is highly stabilized because the hydrophobic aldehyde attacking the *anti*-enamine lies in the hydrophobic region. The excellent enantioselectivities observed can be explained by transition state TS-2. In this case the less favored attack of aldehyde on the *syn*-enamine is more destabilized because the hydrophobic aldehyde lies in the hydrophilic region. Finally, the high diastereoselectivities observed can be explained by transition state TS-3. In this case the attack of aldehyde on *anti*-enamine is more destabilized because the hydrophobic part of the aldehyde is directed towards the hydrophilic region. This model can explain the lower stereoselectivity observed when water is absent.

Host–guest complexes between β-cyclodextrin and 4-substituted proline derivatives were also developed. Catalyst **35** (Figure 24.12) was formed, employing an adamantane proline derivative, and used in 10 mol% [56]. *trans*-4-(4-*tert*-Butylphenoxy)proline **36** (Figure 24.12) was used as catalyst (2 mol%) in the aldol reaction between cyclohexanone and several substituted benzaldehydes in water in the presence of sulfated β-cyclodextrin (10 mol%). Aldol products were obtained in good to high yields and stereoselectivity. It was hypothesized that the aldol reaction occurred in the water phase where organocatalyst **36** resided with sulfated β-CD. Noticeably, this approach allowed the use of a stoichiometric amount of cyclohexanone [57].

24.2.4
Prolinamides

As briefly discussed above, another approach for the modification of the proline structure is its transformation into a prolinamide bearing an appropriate substituent. Apart from simple prolinamide, which catalyzed the self-aldol reaction of

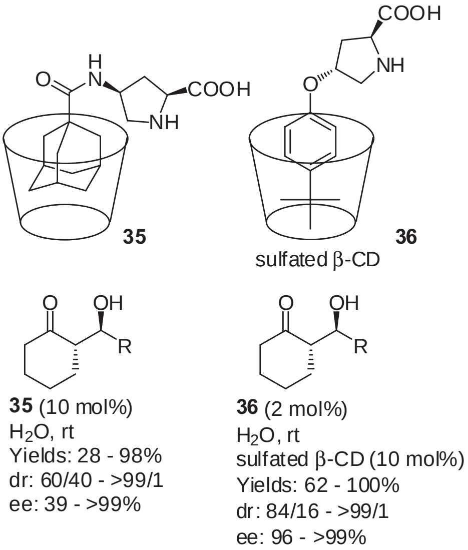


Figure 24.12 Structure of catalysts **35** and **36** and their catalytic activity.

propanal “in water” with good enantioselectivity [58], the amide moiety must contain one of several features: (i) one or more chiral centers, which should match with that of proline, or (ii) an additional coordinating site, or (iii) a hydrophobic group. In several cases, all these features are displayed.

One of the simplest structures is prolinamide **37** (Figure 24.13), which catalyzed the direct aldol reaction of acetone with 4-nitrobenzaldehyde in water in 50% ee. In the absence of water no reaction took place [59]. Further experiments were carried out using proline-thioamide **38** (Figure 24.13). Brine was found to be a suitable reaction medium for the aldol reaction of several cyclic ketones with electron-deficient aldehydes catalyzed by **38** (5 mol%) and in the presence of $Cl_2CHCOOH$ as additive [60].

To obtain better results with hydrophilic ketones such as acetone, new prolinamides bearing the more hydrophobic *gem*-diphenyl group were synthesized (**39**, **40**, Figure 24.13) [28]. Very high yields and enantioselectivities were observed in water for a broad range of aldehydes and ketones without any acid additive, working at −5 or 0 °C. It was observed that yields and ee values were superior in brine to those in water as a “salting out effect” increases the “hydrophobic effect”[28b,c]. Moreover, a detailed study carried out by varying the amount of water using catalyst **41** revealed that water strongly influenced both the rate and enantioselectivity [28c].

Several substituted prolinamides, derived from chiral enantiopure aziridines, of general formula **42** (Figure 24.13), were used in aldol reactions. Optimization of the reaction conditions with cyclic ketones showed that no product was formed when the reaction was carried out in organic solvents such as $CHCl_3$ and DMF.

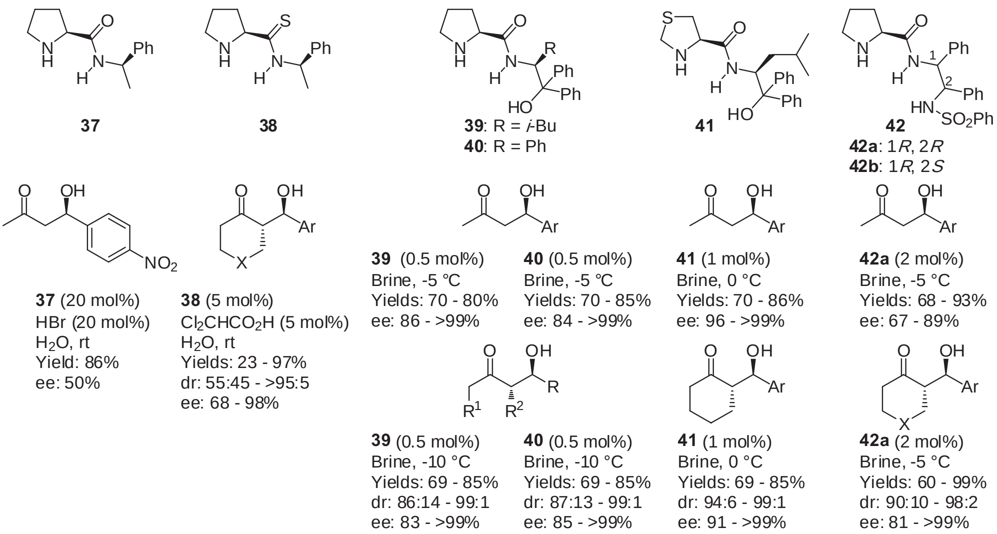


Figure 24.13 Structure of catalysts **37–42** and their catalytic activity.

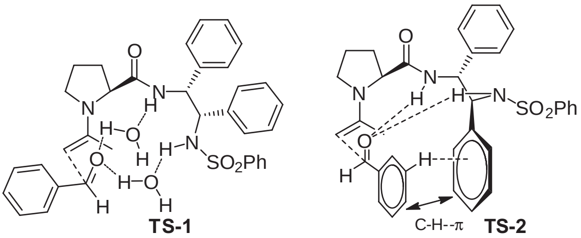


Figure 24.14 Proposed transition states for the aldol reaction catalyzed by **42b**.

Optimal conditions were found when brine was employed as reaction medium at −5 °C [61]. Aldol products were obtained with good to high enantioselectivities when catalyst **42a** was used. These conditions were also used in the reaction with acetone, giving good enantioselectivities. The reaction between acetone and benzaldehyde showed that, when the reaction was carried out in brine, the ee value was high whichever the configuration of C1 and C2 carbon atoms, whereas when the reaction was carried out in neat acetone the ee value was lower when the C2 carbon atom had (*S*) configuration (catalyst **42b**). A model, explaining the role of water for this outcome was given. In particular, when the reaction was carried out in an aqueous medium the water molecules form H-bonding with the amide groups and the aldehyde as shown in TS-1 in Figure 24.14. When the reaction was carried out without water the ee value decreased because of the favorable C–H–π interaction between the phenyl group and hydrogen of the aromatic ring of the benzaldehyde (TS-2) (Figure 24.14).

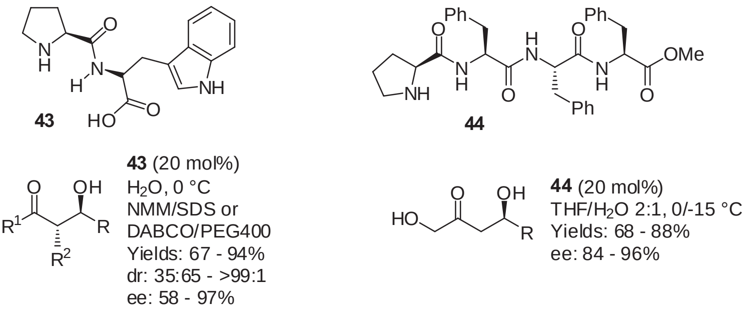


Figure 24.15 Structure of catalysts **43** and **44** and their catalytic activity.

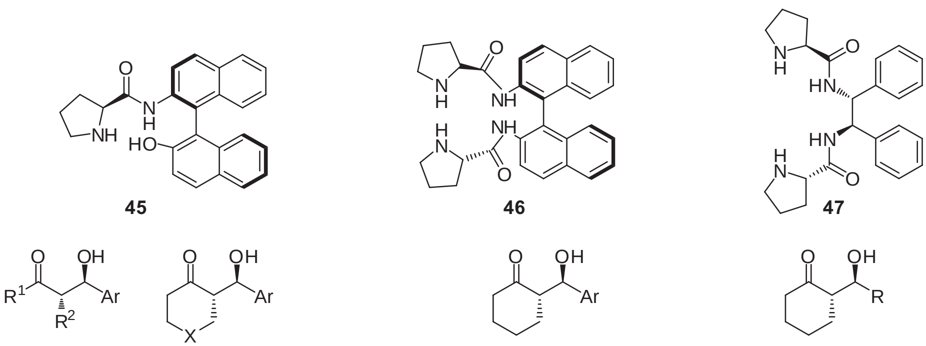
In the dipeptide **43** (Figure 24.15) the additional H-bond could be made by COOH group whereas as the hydrophobic moiety is the tryptophan side-chain. Extensive studies on reaction conditions showed that the presence of a base and a surfactant was essential for success of the reaction. Usually, *N*-methylmorpholine (NMM)/sodium dodecyl sulfate (SDS) or 1,4-diazabicyclo[2.2.2]octane (DABCO)/poly(ethylene glycol) 400 (PEG400) were employed as additive, and the reactions were carried out in water at 0 °C. In the reaction system, the base might form the carboxylate with catalyst, which could increase the solubility in water; the surfactant could increase the interfacial areas of water and organic reagent [62].

The use of water was crucial in controlling the regioselectivity of aldol reactions of aldehydes with hydroxyacetone. When the reaction was catalyzed by L-proline-based small peptide **44** (Figure 24.15), chiral 1,4-diols, which are disfavored products in similar aldol reactions catalyzed by aldolases or L-proline, were obtained as major products [63].

NOBIN-prolinamide **45** (10 mol%, Figure 24.16) in the presence of TFA (10 mol%) as additive gave aldol products in good yields and stereoselectivities [64]. Protection of the hydroxy group of catalyst **45** with a methyl group gave similar results, indicating that the OH group had little influence in the transition state. A different stereochemical outcome was showed by other authors when the reaction was carried out in a different reaction medium in the absence of TFA [65]. Indeed, working in dioxane containing only 1.1 equiv. of water, the methoxy derivative showed lower ee. This different result can be ascribed to the fact that in the different reaction medium (dioxane/water versus water) both NH and OH groups take part in the activation of the aldehyde as H-bond donors. Under the latter conditions high stereoselectivities were observed.

Catalyst **46** (Figure 24.16) was used in 1 : 1 DMF/water mixture [66] or in water in the presence of 20 mol% of benzoic or stearic acid as additive [67]. Prolinamide **47** was used in water in the presence of TFA as additive (Figure 24.16). The latter catalyst was also widely employed with $Zn(OTf)_2$ as additive (5 mol%) under aqueous conditions to give aldols in excellent ee values [68].

A new kind of catalyst is based on the TBDPS-protected D-glucosamine-L-prolinamide **48** (Figure 24.17) [69]. When D-glucosamine [70] or D-glucosamine-L-prolinamide [71] are used as catalyst a poor enantiomeric excess of the aldol



45 (10 mol%)
TFA (10 mol%)
H_2O, rt
Yields: 50 - 99%
dr: 70:30 - 99:1
ee: 62 - 96%

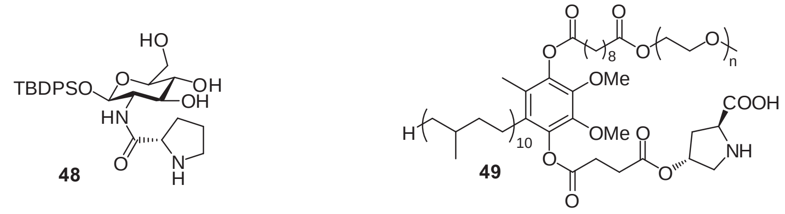
45 (10 mol%)
dioxane:H_2O (1.1 eq)
4 °C
Yields: 26 - 99%
dr: 35:65 - >99:1
ee: 70 - 95%

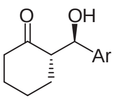
46 (10 mol%)
DMF/H_2O (1:1)
0 °C
Yields: 98 - 99%
dr: 4.3:1 - 10:1
ee: 90 - 93%

46 (10 mol%)
$PhCO_2H$ or stearic acid
(20 mol%)
H_2O (1.1 eq), 2 °C
Yields: 37 - >99%
dr: 50:50 - 99:1
ee: 65 - 93%

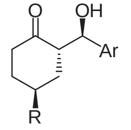
47 (5 mol%)
TFA (10 mol%)
H_2O, 0 °C or rt
Yields: 46 - 99%
dr: 95:5 - 98:2
ee: 92 - 95%

Figure 24.16 Structure of catalysts **45–47** and their catalytic activity.





48 (2 mol%)
Brine, 4 °C
Yields: 86 - >99%
dr: 87:13 - 98:2
ee: 82 - >99%



49 (10 mol%)
H_2O, rt
Yields: 74 - 90%
dr: 68:32 - 90:10
ee: 75 - 97%

Figure 24.17 Structure of catalysts **48** and **49** and their catalytic activity.

product is obtained. These results probably arise because such molecules lack a hydrophobic group in their structure. The presence of the hydrophobic TBDPS group in **48** allows the installation of three different domains: (i) the proline NH catalytic center, (ii) a hydrophobic domain, and (iii) a hydrophilic domain capable of interacting with the aqueous phase. Using catalyst **48** (2 mol%) in brine at 4 °C high stereoselectivities were observed when cyclohexanone was employed as donor. Another example of a molecule bearing hydrophobic and hydrophilic domains is catalyst **49** (Figure 24.17). The catalyst is water-soluble and was employed in water as reaction medium. Moreover, due to its solubility it was recovered in the aqueous phase and recycled [72].

Further examples of prolinamide-based structures do not present any additional chiral center in their structures, but are based on the possibility of establishing an

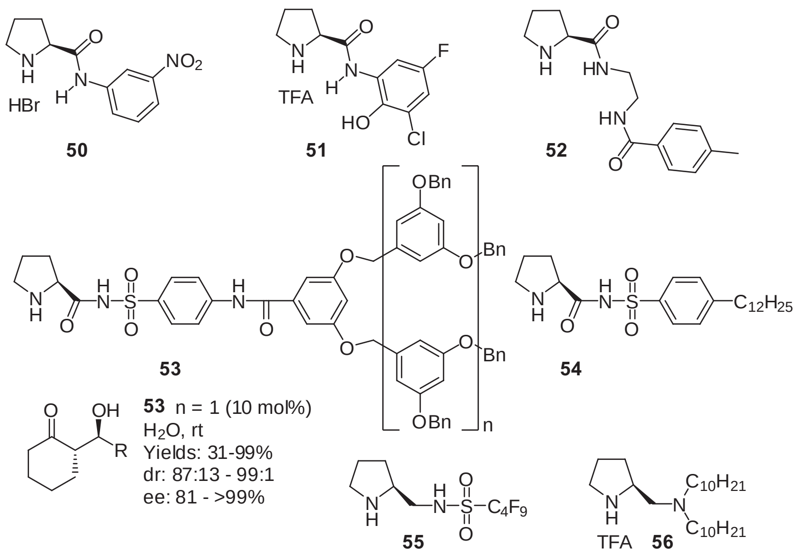


Figure 24.18 Structure of catalysts **50–56** and their catalytic activity.

additional hydrogen bonding or by increasing the acidity of the hydrogen atom of the CONH group. Examples of these catalysts are prolinamide **50**, which was used in high amount (20 mol%) as its HBr salt [73], and prolinamide **51** (Figure 24.18). With the latter catalyst improved enantioselectivities, at the expense of yield, were observed when the reaction medium was changed from $CHCl_3$ to water [74]. In the search for simple prolinamide derivatives able to work in the presence of water, catalyst **52** bearing a substituted ethylenediamine moiety was prepared (Figure 24.18) [75]. The high levels of diastereo- and enantiocontrol observed are again attributed to the formation of hydrogen bonds between the water molecules surrounding the complex and the oxygen of the amide groups, which increase the acidity of the NH groups, making a more compact transition state. The acidity of the hydrogen atom of the CONH group can be enhanced in sulfonamide derivatives. Dendritic catalysts bearing highly hydrophobic groups (**53**, Figure 24.18) showed higher activity and stereoselectivity than similar non-dendritic catalysts bearing less hydrophobic groups. In particular, the second generation catalyst (*n* = 1) provided the best results when used in water [76]. A simpler, still hydrophobic catalyst is sulfonamide **54** (Figure 24.18). This catalyst was used in 20 mol% in $ClCH_2CH_2Cl$ in the presence of one equivalent of water, which had a rate-accelerating effect and with the added benefit of increased diastereoselectivity of the aldol reaction [77]. Moreover, the reaction can be carried out with catalyst loading as low as 2 mol% under neat conditions. A single equivalent of water was still added to improve the reaction rate and selectivity.

A slightly different approach is represented by the use of the fluorous (*S*)-pyrrolidine sulfonamide catalysts **55** (Figure 24.18) [78]. The installation of the

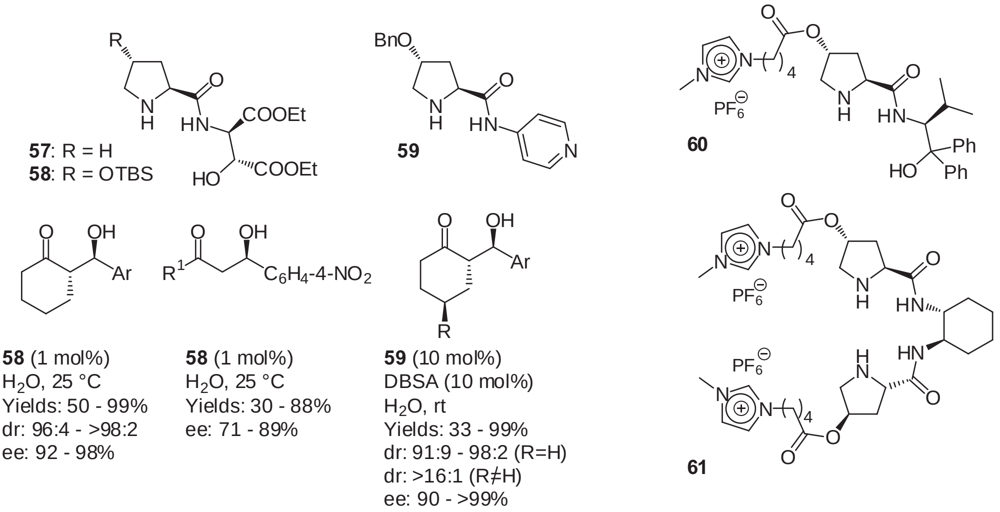


Figure 24.19 Structure of catalysts **57–61** and their catalytic activity.

fluorous moiety presents two advantages: it provides a handle for catalyst recycling by using a fluorous solid-phase extraction technique and its strong electron-withdrawing nature increases the acidity of the NH proton of the sulfonamide, which thus provides a strong hydrogen bonding interaction with the substrate.

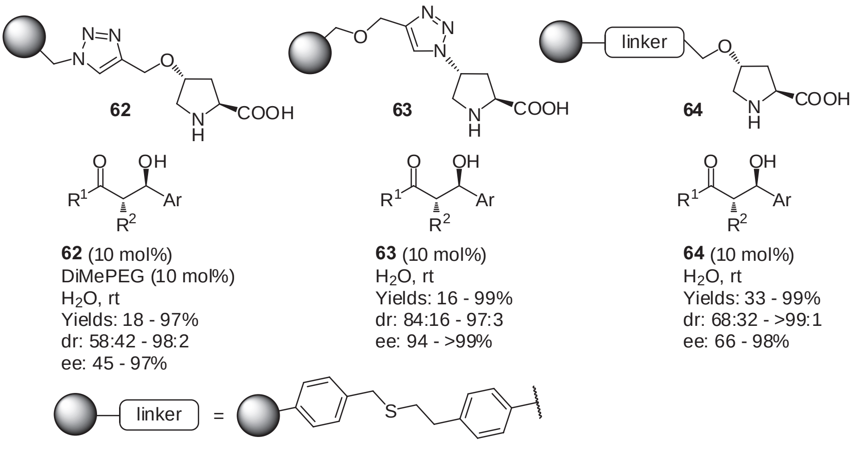
However, the first example of a pyrrolidine-based catalyst working under aqueous conditions reaching a high level of stereoselectivity was the TFA salt of a pyrrolidine derivative bearing long alkyl groups (**56**, Figure 24.18) [79].

As an evolution of type II prolinamide-based catalysts, type III catalysts were prepared. Examples of this kind of modification, catalysts **57** (type II) and **58** (type III), were prepared (Figure 24.19). Catalyst **57** was used in 20–30 mol% in the aldol reactions of aldehydes with hydroxyacetone or fluoroacetone in THF/H_2O (2 : 1) [80]. Excellent enantioselectivities and high regioselectivities, in favor of the usually disfavored 1,4-diol, were observed for hydroxyacetone. In addition, fluoroacetone gave good regioselectivities and high enantioselectivities. Previously, catalyst **57** was used in $CHCl_3$ at −25 °C, furnishing aldol products in good to high stereoselectivities [81]; however, when the more hydrophobic catalyst **58** was used in the reaction between acyclic and cyclic ketones and several aromatic aldehydes in water at 25 °C, high stereoselectivities were obtained with only 1 mol% of catalyst [82]. Coupling the use of water with the highly hydrophobic catalyst **58** gave increased stereoselectivity compared with the use of the less hydrophobic catalyst **57** in $CHCl_3$ at −25 °C. An auto-assembled type III catalyst is prolinamide **59** and surfactant Brønsted acid *p*-dodecyl benzenesulfonic acid (DBSA) (Figure 24.19). DBSA contributed to the enhanced activity and enantioselectivity, most likely by protonating the pyridinyl ring that consequently activated the amide hydrogen-bond donor in hydrophobic micellar media [83].

Examples of type III bearing ionic liquid tags are catalysts **60** and **61** (Figure 24.19). These catalysts were employed in water in 1–5 mol% (**60**) or 10 mol% (**61**) and the presence of the ionic liquid tag enabled their recovery [84].

24.2.5
Supported Proline and Proline Derivatives

Highly hydrophobic supports, such as polystyrene, linked at the 4-position of proline may be regarded as a large apolar substituent and, as for 4-substitued proline derivatives, could favor stereocontrol of the aldol reaction in water. A polystyrene support was linked to 4-hydroxyproline using a 1,2,3-triazole spacer in catalysts **62** and **63** (Figure 24.20). Water gave better stereoselectivities than DMSO, DMF, or neat conditions when catalyst **62** was employed. Poly(ethylene glycol) dimethyl ether (DiMePEG) was used as additive with the aim of increasing the yields [85]. Catalyst **63** behaved as an artificial aldolase because it was able to swell in water despite the hydrophobicity of the polymer backbone. The swollen resin showed a water content up to 24 wt%, building in such a way an aqueous microenvironment. This material parallels the effect of essential water for some natural enzymes used in organic media. Indeed, it was demonstrated that only the water molecules that swelled the resin gave the catalytic properties to this material. This property arose from the formation of a hydrogen-bond network connecting the proline and 1,2,3-triazole linker. Catalyst **63** was used in 10 mol% without any additive to give aldol products in high stereoselectivity [86]. Catalyst **64** (Figure 24.20) both promoted "on water" and "in the presence of water" aldol reactions [87]. In fact, aldol reactions took place only when water was used. This solvent effect, coupled with the high stereoselectivities observed, was explained by the formation of a hydrophobic core in the inner surface of the resin whereas the hydrophilic proline moiety lies in the interface resin/water. Such a



62 (10 mol%)
DiMePEG (10 mol%)
H_2O, rt
Yields: 18 - 97%
dr: 58:42 - 98:2
ee: 45 - 97%

63 (10 mol%)
H_2O, rt
Yields: 16 - 99%
dr: 84:16 - 97:3
ee: 94 - >99%

64 (10 mol%)
H_2O, rt
Yields: 33 - 99%
dr: 68:32 - >99:1
ee: 66 - 98%

Figure 24.20 Structure of supported catalysts **62–64** and their catalytic activity.

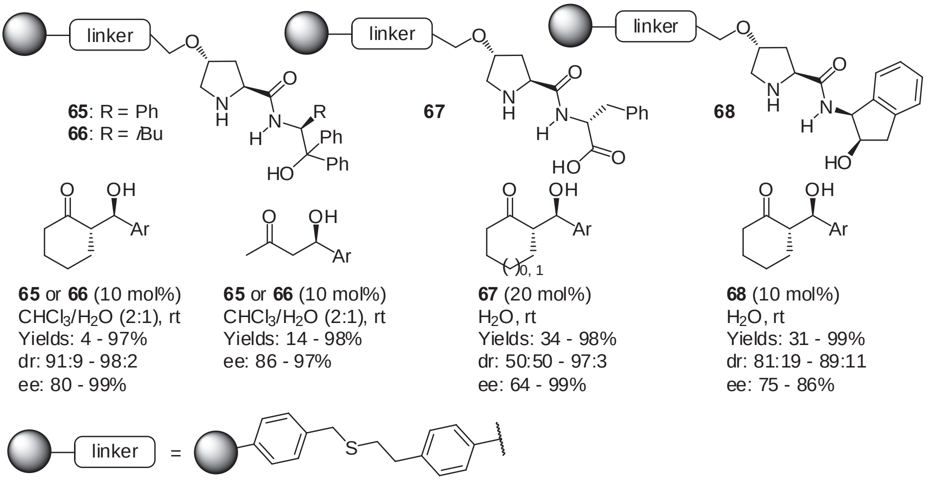


Figure 24.21 Structure of supported catalysts **65–68** and their catalytic activity.

microenvironment both promoted the aldol reaction and increased the stereoselectivity. The authors hypothesized that solvents such as DMSO or DMF do not promote the reaction simply because they are good solvents. Ketones and aldehydes are well dissolved while the catalytic center is supported on a material having a very low surface area. This strongly favors the repartition of the reactants in the liquid phase. When water is used as reaction medium, the reactants are forced into the hydrophobic pocket of the resin.

Water both increased yields and stereoselectivities when used as co-solvent with DMF or in ketone/water mixtures in the aldol reaction catalyzed by other polystyrene-supported proline catalysts [88]. The excellent results obtained with prolinamides **39** and **40** prompted several researchers to investigate their immobilization. When supported catalysts **65–66** (Figure 24.21) were used in organic solvents such as $CHCl_3$, CH_2Cl_2, tetrahydrofuran, toluene, and diethyl ether very low yields were observed. In contrast, when the above solvents were used as a 1 : 2 (v/v) water/solvent mixture the reaction took place with high ee values. The optimal reaction conditions were found with a 1 : 2 (v/v) water/chloroform mixture. This mixture was the best compromise between the good swelling properties of chloroform and the formation of a concentrated organic phase due to the presence of water [89].

Unsupported dipeptides such as **43** were active only in the presence of NMM/SDS or DABCO/PEG400. Immobilization of several proline-based dipeptides showed that there is no need for such additives. For instance, resin **67** (Figure 24.21) worked nicely in water at room temperature without additive [90]. The role of the support was evident when performances of supported catalyst **68** (Figure 24.21) in water were compared to those of the corresponding unsupported catalyst. In the latter case, stereoselectivities were much lower with respect to those obtained

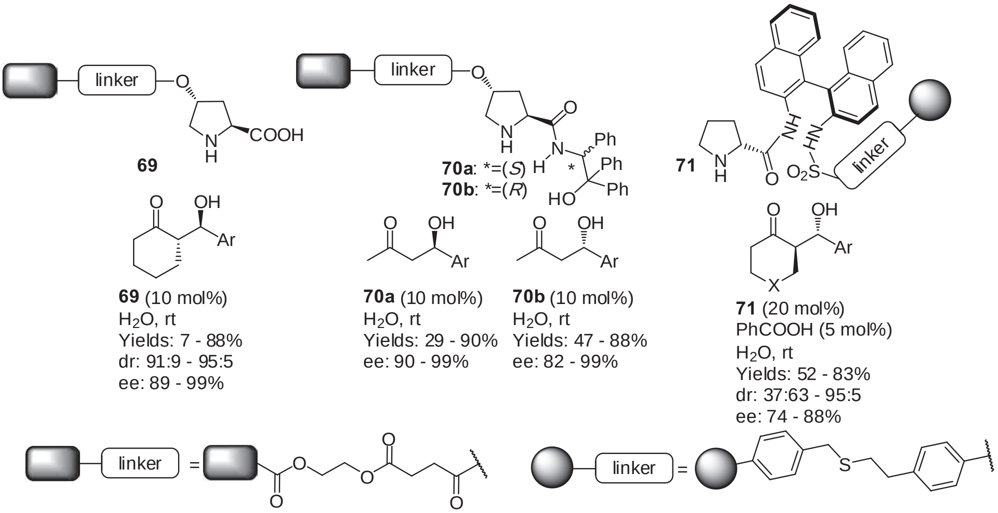


Figure 24.22 Structure of supported catalysts **69–71** and their catalytic activity.

with **68** [90]. While resins **62–68** were prepared following a post-modification approach, resins **69** and **70** (Figure 24.22) were prepared in a bottom-up fashion from methacrylic functional monomers and used in 10 mol% loading in the aldol reaction between acetone or cyclohexanone with substituted benzaldehydes at room temperature in water [91].

A different approach for proline immobilization is the use of the appropriate prolinamide moiety for anchorage. Following this approach and using again a post-modification methodology, the polystyrene-supported *N*-sulfonyl-(*R*a)-binam-prolinamide catalyst **71** was prepared (Figure 24.22). This catalyst was used in water in 20 mol% loading using benzoic acid as additive (5 mol%) [92]. Diastereoisomers having an *anti* configuration were obtained except when cyclopentanone was used. However, reaction times were long (1–10 days).

24.3
Michael Reactions

In Michael reactions, water can also be used as simple additive or as the sole reaction medium. Water was used as additive (10 equiv.) to increase the efficiency and circumvent the need to add an acidic additive. In addition, water would facilitate hydrogen bonding and proton transfer that could improve the enantioselectivity. The most useful catalysts are based on the pyrrolidine structure. The pyrrolidine may possess a large hydrophobic substituent at C2 or may be capable of establishing a H-bond with the acceptor molecule. Such a H-bond may be formed because of the presence of an acid hydrogen atom in the structure, or because of the

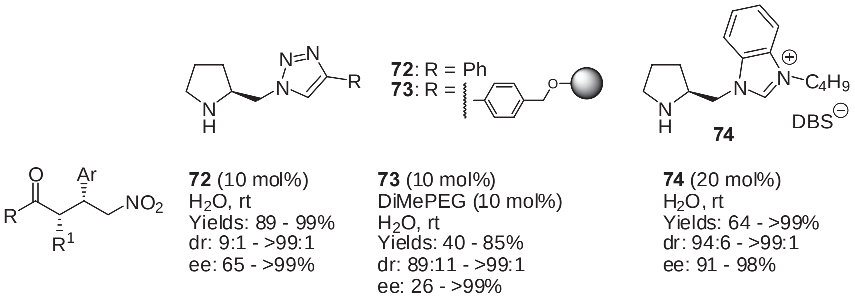


Figure 24.23 Structure of catalysts **72–74** and their catalytic activity.

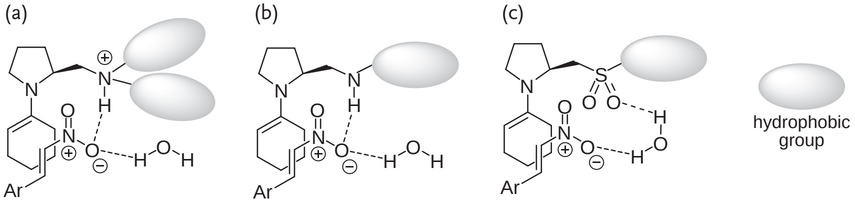


Figure 24.24 Proposed role of water in pyrrolidine-based catalysts in the addition of cyclohexanone to nitrostyrenes.

presence of an acid additive or because of the presence of water molecules. These approaches will be discussed.

There are several reports on the use of secondary amine-based catalysts in water as the sole reaction medium. Pyrrolidine-triazole catalyst **72** (Figure 24.23) gave high stereoselectivities in the Michael addition of cyclohexanone or acetone to nitrostyrenes. The reactions proceeded smoothly both in $CHCl_3$ and water. However, the aqueous medium promoted the process more efficiently, pushing the reactions to completion within a shorter time. Each reaction was carried out in both reaction media, revealing that water generally gave better reactivity and enantioselectivity [93].

A polymer-supported version of the above catalyst, resin **73** (Figure 24.23), was also used for the same reactions. Also in this case, water was the reaction medium of choice, while the use of DiMePEG as additive led to greater improvement in both conversion and in stereoselectivity [94].

The ionic liquid-type compound **74** having the *p*-dodecyl benzene-sulfate (DBS) anion worked well in the Michael addition of cyclohexanone to nitrostyrenes in water (Figure 24.23). No organic solvents or additional additives were used. This surfactant-type organocatalyst gave high yields and stereoselectivities under these conditions. Interestingly, the Michael products could be separated from the bulk water without using any organic solvent [95].

Pyrrolidine-based catalysts possessing a tertiary amine functionality were usually employed in the presence of an acid additive. Protonation of the tertiary nitrogen atom can furnish the H-bond donor (Figure 24.24a). Pyrrolidine-based catalyst **56**

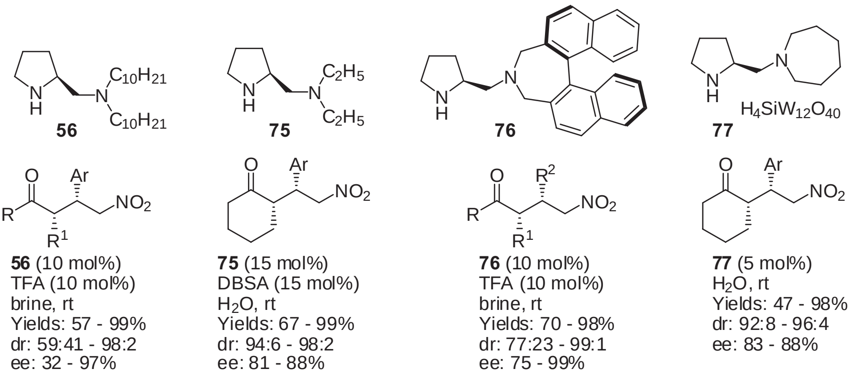


Figure 24.25 Structure of catalysts **56** and **75–77** and their catalytic activity.

used in the aldol reaction also worked very well in the Michael reaction of ketones and aldehydes with nitrostyrenes (Figure 24.25). Brine, as reaction medium, improved the yield and stereoselectivity compared to reaction in organic solvent or water [96]. Instead of having long alkyl chains, pyrrolidine **75** possesses two short ethyl chains, but was still used in the presence of the surfactant Brønsted acid DBSA (Figure 24.25). Such a combination was investigated by light microscopy studies, which demonstrated that a good colloidal dispersion was formed in pure water [83]. The Michael addition of cyclohexanone to nitrostyrenes gave adducts in high yields and diastereoselectivities, although enantioselectivities were <90%. The highly hydrophobic chiral diamine **76** (Figure 24.25) was tested in several solvents. Brine, with TFA as additive, was the best reaction medium. Other solvents such as DMSO or toluene gave poor enantioselectivity, while high yields and stereoselectivities were obtained with organic solvents such as MeCN, $CHCl_3$, CH_2Cl_2, MeOH, EtOH, and *i*-PrOH. Again, the high yields and stereoselectivities in aqueous medium were explained by the hydrophobic environment created by the binaphthyl group [97]. Catalyst **77** (Figure 24.25) was used both under neat and aqueous conditions. Much less cyclohexanone was used under the latter conditions, showing the advantage of the aqueous system [98].

The fluorous pyrrolidine sulfonamide **78** (Figure 24.26) displayed great activity in water as a result of enhanced aggregation between the catalyst and the substrates in the aqueous environment. High yields and stereoselectivities were obtained [99]. In this case the enhanced acidity of the N–H hydrogen atom permits avoidance of the acid additive (Figure 24.24b). In addition, the simple pyrrolidine-thiourea catalyst **79** (Figure 24.26) was found to be active in the asymmetric Michael addition of cyclic ketones to nitrostyrenes when the reactions were carried out in water with benzoic acid (10 mol%) as additive at 35 °C [100]. 2-Aminobenzimidazole is a more conformationally rigid H-bond donor than thiourea. Such a moiety was introduced in catalyst **80** and used in water in the presence of a co-catalyst (Figure 24.26). Except for the addition product between

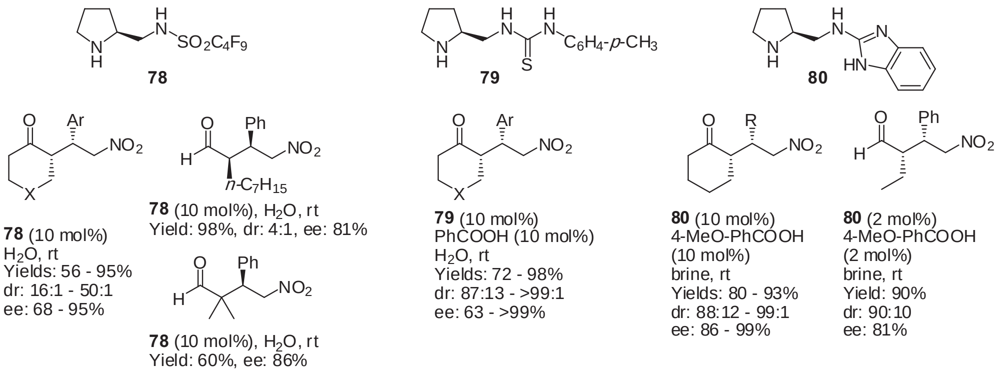


Figure 24.26 Structure of catalysts **78–80** and their catalytic activity.

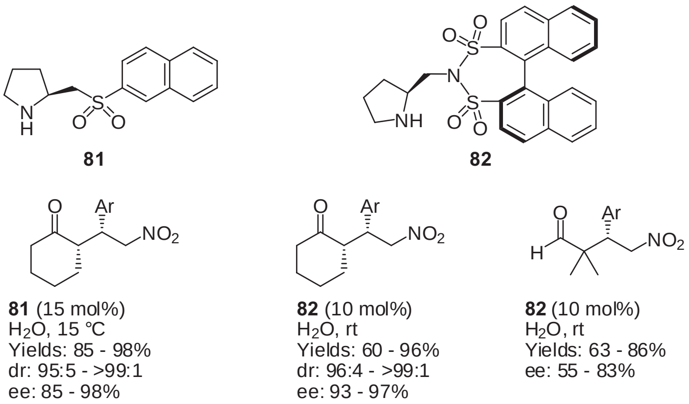


Figure 24.27 Structure of catalysts **81** and **82** and their catalytic activity.

acetone and nitrostyrene, which afforded Michael adduct in low ee value, enantio- and diastereoselectivities were high [101].

Pyrrolidine compounds **81** [102] and **82** [103] (Figure 24.27) do not possess H-bond donor moieties; however, the oxygen atom of the sulfone functionality in combination with a protic solvent, such as water, could provide a H-bond interaction (Figure 24.24c). In such a way the use of the additive was avoided.

Diarylprolinol **83** (Figure 24.28) was used in the addition of aldehydes to 3-nitroacrylates and aryl- and alkyl-substituted nitroalkenes [104]. Water was the reaction medium of choice with benzoic acid as additive to improve the reaction rate and diastereoselectivity. Under these conditions high stereoselectivities were observed. Diarylprolinol **84** (Figure 24.28) was developed with the aim of having a water-soluble catalyst that is easily recoverable in water. Catalyst **84** may be used

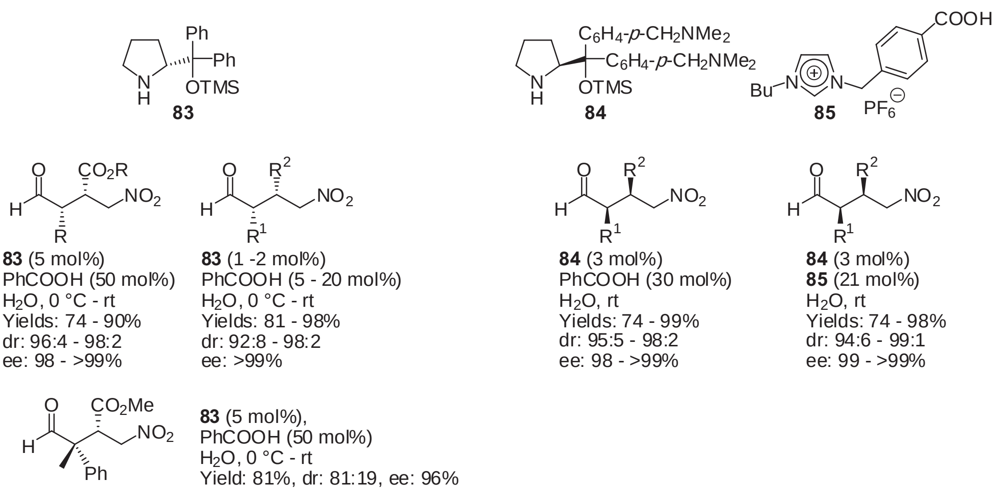


Figure 24.28 Structure of catalysts **83** and **84** and their catalytic activity.

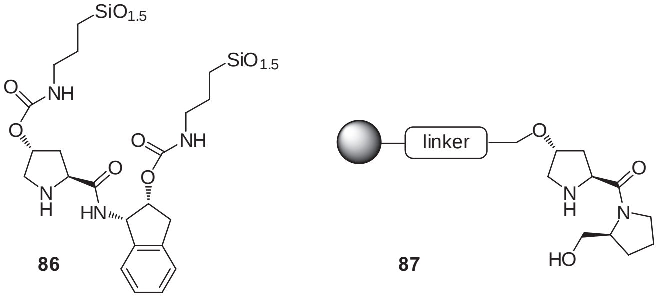


Figure 24.29 Structure of supported catalysts **86** and **87**.

in only 3 mol% in the presence of benzoic acid [105] or in the presence of ionic liquid acid **85** [106]. In each case a high level of stereoselectivities were achieved. In addition, a superparamagnetic nanoparticle-supported (*S*)-diphenylprolinol trimethylsilyl ether was synthesized and applied for the asymmetric Michael addition of aldehydes to nitroalkenes in water [107].

In addition to pyrrolidine-based structure, proline-based catalysts were also investigated. Two examples of supported prolinamide-based catalysts for the Michael reaction are **86** and **87** (Figure 24.29). Prolinamide-bridged silsesquioxane **86** was prepared from a bis-silylated prolinamide by sol–gel methodology and used in water. This catalytic material was also used in aldol reactions [108]. The prolyl-prolinol catalyst **87** was anchored to a polystyrene backbone and used in a dichloromethane/water mixture [22a].

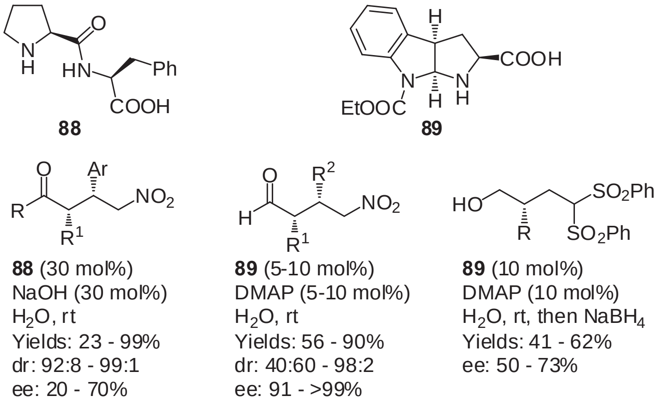


Figure 24.30 Structure of catalysts **88** and **89** and their catalytic activity.

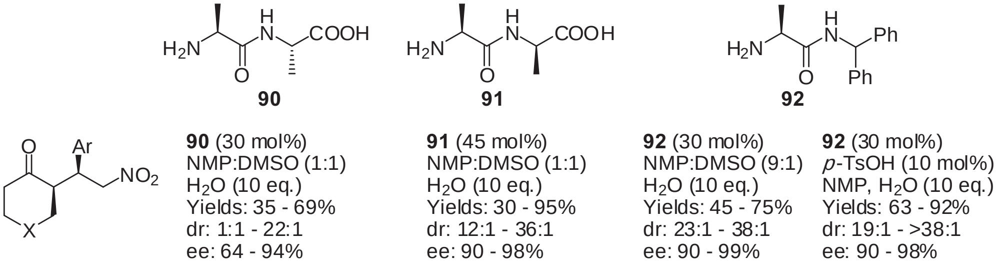
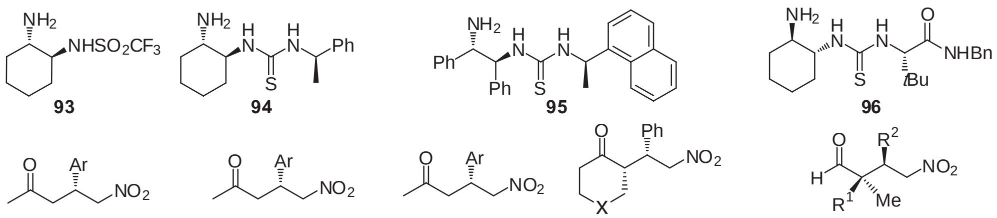


Figure 24.31 Structure of catalysts **90–92** and their catalytic activity.

Two examples of unsupported proline-based catalysts are compounds **88** and **89** (Figure 24.30). Dipeptide **88** was used in water in the presence of NaOH in the addition of ketones to nitroalkenes. The presence of sodium hydroxide additive was crucial for the success of the reaction [109]. Catalyst **89** was designed on the structurally rigid hexahydropyrrolo[2,3]indole skeleton and efficiently catalyzed the enantioselective addition of aldehydes to nitroalkenes both in methanol and water [110]. The same catalyst was also used in the addition of aldehydes to vinyl sulfone followed by reduction with sodium borohydride. In this case water was a better reaction medium than methanol [111].

Good results were also obtained with primary amine catalysts. In such cases, however, organic solvents were employed and water was used in low amount (15–500 mol%) but its presence allowed significant improvements. Then, using *N*-methylpyrrolidone/DMSO as solvent and water as additive, simple dipeptides, such as (*S*)-ala-(*S*)-ala (**90**) and (*S*)-ala-(*R*)-ala (**91**) [112] or alanine derivative **92** [113] were employed in the Michael addition of ketones to nitrostyrenes (Figure 24.31). Lower stereoselectivities were observed when hydroxyacetone or butanone were used.



93 (15 mol%)
$CHCl_3/H_2O$ (15 mol%)
Yields: 64 - 94%
ee: 57 - 87%

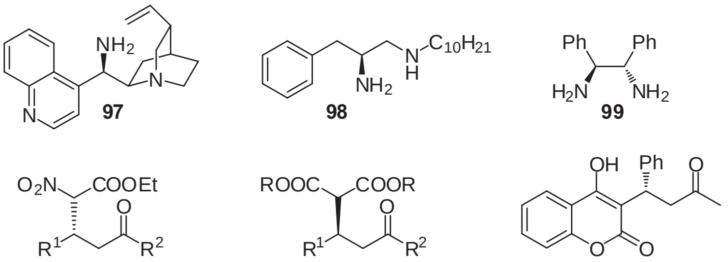
94 (15 mol%)
AcOH (15 mol%)
Toluene/H_2O
(200 mol%)
Yields: 85 - 93%
ee: 84 - 92%

95 (15 mol%)
AcOH (15 mol%)
Toluene/H_2O
(200 mol%)
Yields: 84 - 99%
ee: 90 - 91%

95 (15 mol%)
AcOH (15 mol%)
Toluene/H_2O (200 mol%)
Yields: 84 - 99%
dr: 80:20 - 83:17
ee: 98 - >99%

96 (20 mol%)
CH_2Cl_2/H_2O
(500 mol%)
Yields: 34 - 98%
dr: 2.1:1 - >50:1
ee: 94 - 99%

Figure 24.32 Structure of catalysts **93–96** and their catalytic activity.



97 (20 mol%)
PhCOOH (40 mol%)
H_2O, rt
Yields: 93 - 98%
ee: 65 - 93%

98 (20 mol%)
TFA (20 mol%)
H_2O 50 °C
Yields: 39 - 98%
ee: 76 - 98%

99 (2 mol%)
PhCOOH (4 mol%)
H_2O, rt, ultrasound
Yield: 78% ee: 70%
(ee >99% after crystallization)

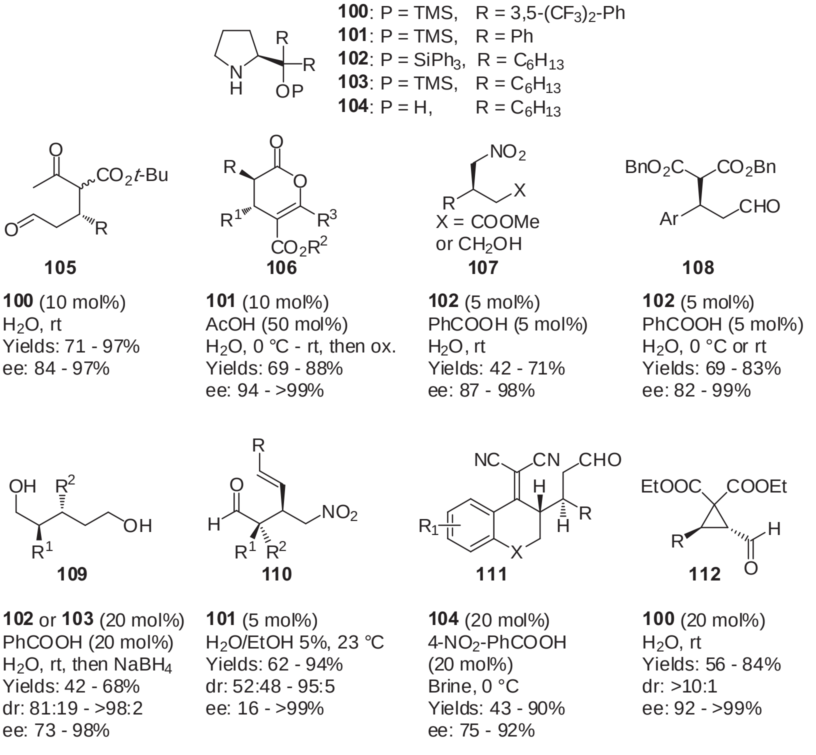
Figure 24.33 Structure of catalysts **97–99** and their catalytic activity.

The enantioselective addition of ketones to nitrostyrenes was developed by using the bifunctional sulfonamide primary amine catalyst **93** (Figure 24.32). No reaction took place when water was used as reaction medium. The best solvent was $CHCl_3$. However, addition of water increased the yield and enantioselectivity, probably because it increased catalyst turnover due to facilitating the release of the primary amine catalyst from the imine. Moreover, the authors reported an explanation of the role of water in the enhancement of enantioselectivity [114]. Three different primary thiourea-based catalysts (**94–96**) were also used with very good results (Figure 24.32) [115–117].

Water as the sole reaction medium was used with other primary amines. 9-Amino-9-deoxyepicinchonine (**97**) was used in the enantioselective conjugate addition of α-nitroacetate to α,β-unsaturated ketones (Figure 24.33). The catalyst was employed in a large amount (20 mol%) in the presence of an even larger amount of additive (40 mol%) [118]. Malonates were added to α,β-unsaturated ketones in the presence of amine **98** (20 mol%) and TFA (20 mol%) (Figure

24.33). Enantioselectivities were high even if reactions were carried out at 50 °C. However, long reaction times were needed [119]. Diamine **99** in only 2 mol% and benzoic acid in 4 mol% catalyzed the synthesis of warfarin in water at room temperature, in an ultrasound bath, in good yield and a good level of enantioselectivity (70%, Figure 24.33). Crystallization from hexane gave optically pure warfarin [120].

Diarylprolinol-based catalysts have found extensive application in synthesis and their use in water has been successful. In addition to the examples described in Figure 24.28, other examples are reported here. These catalysts were designed following the idea of the favorable role played by hydrophobic aryl or alkyl chains in water-compatible enamine-mediated catalysis and the assumption that for effective control of iminium geometry and face shielding a bulky group should be located near the nitrogen atom of the catalyst. Catalyst **100** worked well in the Michael addition of *tert*-butyl-3-oxo-butyric ester with α,β-unsaturated aldehydes under neat conditions or using water as reaction medium to furnish compounds **105** (Figure 24.34) [121]. Enantioselective synthesis of tetrasubstituted dihydropyrones **106** (Figure 24.34) through the cyclization of aldehydes and α-keto-α,β-unsaturated esters was accomplished in water media by using catalyst **101** [122].



100: P = TMS, R = 3,5-$(CF_3)_2$-Ph
101: P = TMS, R = Ph
102: P = $SiPh_3$, R = C_6H_{13}
103: P = TMS, R = C_6H_{13}
104: P = H, R = C_6H_{13}

105
100 (10 mol%)
H_2O, rt
Yields: 71 - 97%
ee: 84 - 97%

106
101 (10 mol%)
AcOH (50 mol%)
H_2O, 0 °C - rt, then ox.
Yields: 69 - 88%
ee: 94 - >99%

107
102 (5 mol%)
PhCOOH (5 mol%)
H_2O, rt
Yields: 42 - 71%
ee: 87 - 98%

108
102 (5 mol%)
PhCOOH (5 mol%)
H_2O, 0 °C or rt
Yields: 69 - 83%
ee: 82 - 99%

109
102 or **103** (20 mol%)
PhCOOH (20 mol%)
H_2O, rt, then $NaBH_4$
Yields: 42 - 68%
dr: 81:19 - >98:2
ee: 73 - 98%

110
101 (5 mol%)
H_2O/EtOH 5%, 23 °C
Yields: 62 - 94%
dr: 52:48 - 95:5
ee: 16 - >99%

111
104 (20 mol%)
4-NO_2-PhCOOH
(20 mol%)
Brine, 0 °C
Yields: 43 - 90%
ee: 75 - 92%

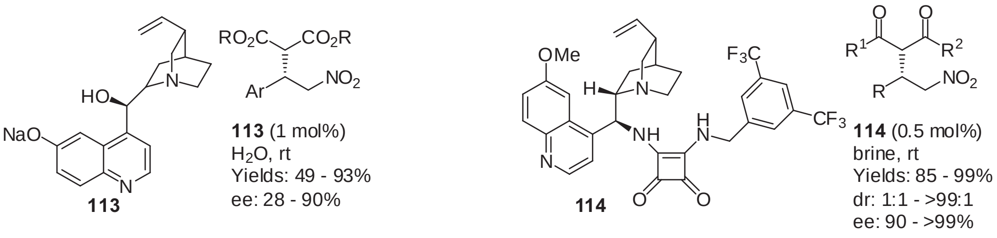
112
100 (20 mol%)
H_2O, rt
Yields: 56 - 84%
dr: >10:1
ee: 92 - >99%

Figure 24.34 Structure of catalysts **100–104** and their catalytic activity.

High stereoselectivities were observed when **102** was used in water, with benzoic acid as additive, in the addition of nitromethane or benzyl malonate or aldehydes to α,β-unsaturated aldehydes to give products **107–109** (Figure 24.34) [123]. Addition of aldehydes to α,β,γ,δ-unsaturated nitro compounds in the presence of 5 mol% of catalyst **101** gave products **110** in high stereoselectivities. In this case a mixture of ethanol and water (5 vol.%) was used. Good results were also obtained using beer as reaction medium whereas the more alcoholic white wine gave lower stereoselectivity [124]. In addition, the direct vinylogous Michael addition reaction of vinylmalononitriles to α,β-unsaturated aldehydes was carried in aqueous medium to give compounds **111.** Screening of five dialkyl-(*S*)-prolinols showed that catalyst **104** gave high yields and ee values when employed in brine at 0 °C with 4-nitrobenzoic acid as additive (Figure 24.34) [125].

Cyclopropanation of α,β-unsaturated aldehydes with diethyl bromomalonate, proceeding via a cascade Michael/α-alkylation process, was carried out in the presence of catalyst **100** in water to give compounds **112** (Figure 24.34). This is a case of an "on water" organocatalytic reaction. Indeed, organic solvents such as $CHCl_3$ or THF gave comparable levels of stereoselectivities but lower yields with respect to water [126].

A different organocatalyst, not based on amino acid derivatives, was successfully employed in the asymmetric addition of malonate to nitrostyrenes. Reactions catalyzed by sodium demethylquinine salt **113** proceeded in either organic solvent (THF or toluene) or water, giving the product in high yield (Figure 24.35). However, water gave higher enantioselectivity than organic solvents. Moreover, the enantioselectivity depended significantly on the concentration of the substrate in water. Catalyst **113** was used for a set of substrates in only 1 mol% loading, giving product from moderate to high ee [127]. The enantioselective addition of 1,3-dicarbonyl compounds to nitroalkanes was achieved using the bifunctional cinchona-based squaramide **114** (Figure 24.35), a H-bond mediated organocatalyst. Using water as a solvent in H-bonding-mediated asymmetric catalysis is a challenge because water can interfere due to its capacity to disrupt hydrogen bonds. However, reactions in brine were highly accelerated compared to those carried out in CH_2Cl_2 and products were isolated with high ee values [128].



113

113 (1 mol%)
H_2O, rt
Yields: 49 - 93%
ee: 28 - 90%

114

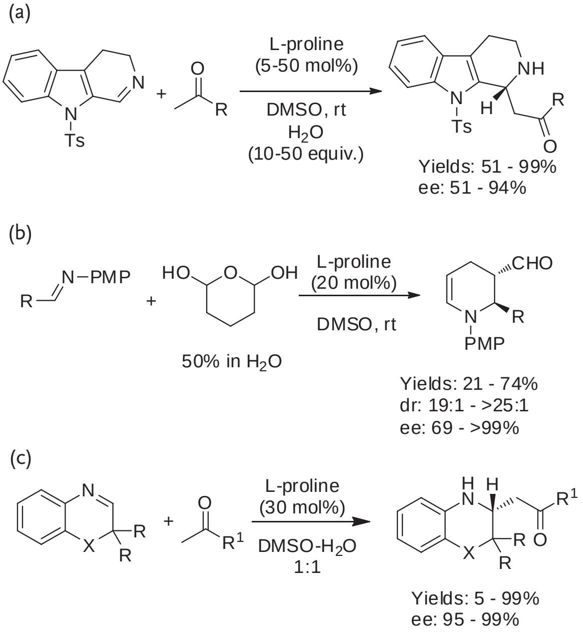
114 (0.5 mol%)
brine, rt
Yields: 85 - 99%
dr: 1:1 - >99:1
ee: 90 - >99%

Figure 24.35 Structure of catalysts **113** and **114** and their catalytic activity.

24.4
Mannich Reaction

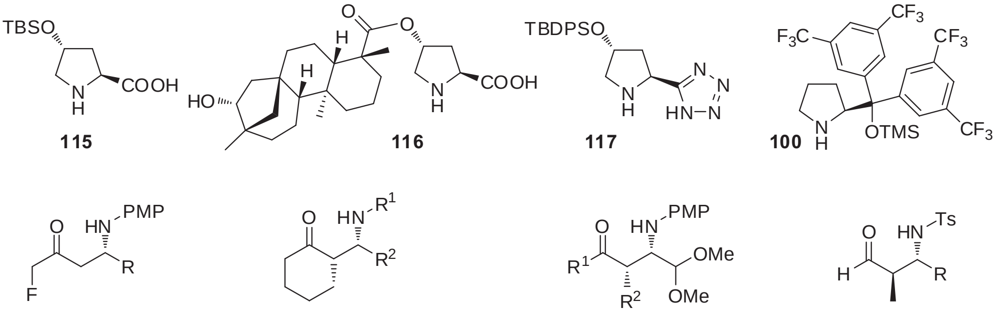
The direct asymmetric Mannich reaction represents a convenient route for the synthesis of optically active α- or β-amino acid derivatives and γ-amino alcohols [129]. In addition, Mannich adducts can be further transformed into various bioactive molecules such as β-lactams, amino sugars, imino sugars, and amino alcohols [130]. In the literature, several recent examples reporting the use of variable amounts of water in the organocatalyzed enantioselective Mannich reaction have been reported.

Small amount of water (10–50 equiv.) are able to affect the stereoselectivity of the products between 9-tosyl-3,4-dihydro-β-carboline and ketones in the presence of L-proline as a catalyst in DMSO (Scheme 24.5a) [131]. This effect was also observed in CH_2Cl_2 and acetone, although it cannot be fully rationalized. Later, proline gave rise to high stereoselectivities in the catalytic reaction of aqueous tetrahydro-2*H*-pyran-2,6-diol with *N*-(*p*-methoxyphenyl) (PMP) aldimines in DMSO to afford the corresponding tetrahydropyridines via a Mannich-type/intramolecular cyclization cascade reaction (Scheme 24.5b) [132].



Scheme 24.5 Proline-catalyzed Mannich reactions.

Mannich addition of ketones to chalcogenazines with excellent enantioselectivities has been recently reported (Scheme 24.5c) [133]. The presence of an equal amount of water greatly accelerated the reaction, which was accomplished in just



115 (20 mol%)
DMF/H_2O (3 eq), 4 °C
Yields: 53 - 81%
ee: 94 - >99%

116 (10 mol%)
H_2O, rt
Yields: 38 - >99%
dr: 44:56 - >99:1
ee: 37 - >99%

117 (10 mol%)
H_2O, 0 °C
Yields: 58 - 93%
dr: 2.9:1 - >20:1
ee: 88 - 97%

100 (10 mol%)
Brine,10°C
Yields: 9 - >99%
dr: 71:29 - >95:5
ee: 84 - 98%

Figure 24.36 Structure of catalysts **115–117** and **100** and their catalytic activity in the Mannich reaction.

one day instead of seven. Interestingly, the corresponding monolithic polystyrene-supported proline has also been prepared, which was in turn tested in the title reaction but exhibited minor activity (4 days) and selectivity. However, the heterogeneous system was found to be recyclable for ten cycles.

4-Silyloxy-proline **115** was the catalyst in a three-component Mannich reaction employing fluoroacetone as donor (Figure 24.36) [134]. The reported protocol allowed access to pharmaceutically important enantiopure fluorinated β-amino ketones. Six isosteviol-amino acid conjugates have been screened as amphiphilic organocatalysts for the asymmetric three-component Mannich reaction of cyclohexanone and anilines with aromatic aldehydes in the presence of water [135]. Among them, **116** was the most active, and its high selectivity has been justified in terms of hydrophobic and hydrophilic regions formed by the catalyst in the aqueous media.

On the other hand, siloxy-tetrazole hybrid catalyst **117** proved to be active in the Mannich reaction, affording *syn*-adducts with good to excellent yield and enantioselectivity in the presence of water and without organic solvent [136]. In addition, the sodium salt of 4-TBDPSO-proline **23** is also an effective Mannich catalyst for α-imino glyoxylate [136]. Recently, an asymmetric Mannich reaction catalyzed by diarylprolinol silyl ether **100** to afford the *anti*-Mannich product with excellent enantioselectivity was developed [137]. The reactions proceeded through a cascade sequence in which the first event was the desulfonative preparation of *N*-Ts imines starting from the corresponding sulfonamidosulfone. In the presence of water, the gradually generated imine readily reacted with the enamine forming the adducts.

A three-component Mannich reaction of *O*-benzyl hydroxyacetone with *p*-anisidine and aldehydes was carried out using the TBDPS-protected L-threonine catalyst **118** (Figure 24.37), which gave the best results among a series of catalysts

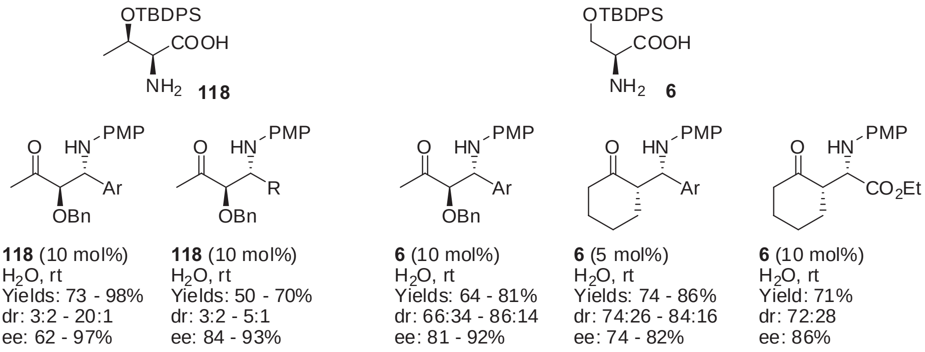


Figure 24.37 Structure of catalysts **118** and **6** and their catalytic activity in the Mannich reaction.

investigated [138]. The reaction was carried out using water as the sole reaction medium with good to high stereoselectivities in the case of both arylaldehydes and aliphatic aldehydes. Later, a TBDPS-protected L-serine catalyst (**6**) was used under the same conditions for the above reactions, giving good stereoselectivities [139].

24.5
Diels–Alder Reaction

The Diels–Alder reaction, a [4+2] cycloaddition, is one of the most studied organic reactions and gives rise six-membered products via carbon–carbon bond formation. Notably, it was the first organic reaction run in water, by Otto Diels and Kurt Alder themselves in 1931 [140], and from its rediscovery in 1980 by Breslow [14d] to now a huge number of reports on the issue have been published. Curiously, water was also used, in mixture with methanol, in one of the first reports on organocatalysis, in 2000 [141]. MacMillan showed that 5% of water in methanol, in the presence of HCl as additive, boosted both the reaction rate and the enantioselectivity in the asymmetric Diels–Alder reaction between dienes and α,β-unsaturated aldehydes catalyzed by **119**, probably facilitating iminium ion hydrolysis during the catalytic step (Figure 24.38). The same group showed that only water, in the presence of $HClO_4$, was a suitable reaction medium for the title process, with **120** (20 mol%) being the best catalyst [142]. Several years later, the use of water as reaction media improved the reaction rate and enantioselectivity when **100** · $HClO_4$ was used as catalyst, while brine slowed it down and limited the selectivity, showing that salting out is detrimental to this process [143]. *N*-Methylpyridinium triflate, mpy(OTf), ionic liquid and water (3 : 1) were used to carry out the Diels–Alder cycloaddition in the presence of only 3 mol% of **119** [144]. Interestingly, in some cases superior selectivity, product yield, and shorter reaction times were observed in comparison with classical organic solvents. Water plays a

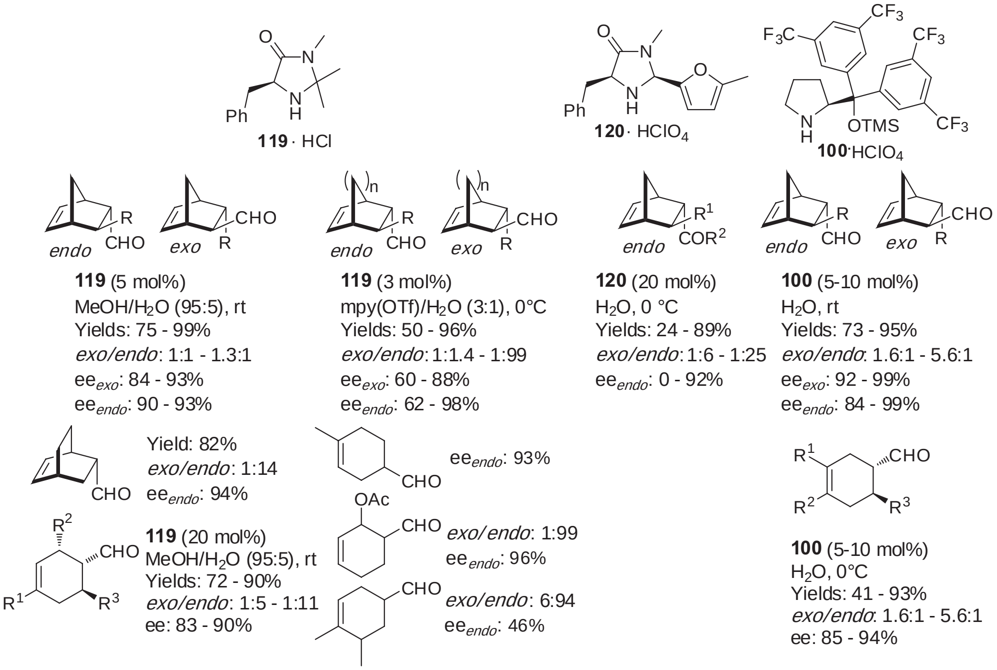


Figure 24.38 Structure of catalysts **119** and **120** and **100** and their catalytic activity in the Diels–Alder reaction.

fundamental role in this reaction both as the co-solvent, allowing a homogeneous phase for transformations carried out in mpy(OTf), and for mechanistic reasons in facilitating the iminium ion hydrolysis.

On the other hand, cyclic hydrazide catalysts **121**·TfOH [145] and **122**·TfOH [146] were active in Diels–Alder reactions of cyclopentadiene and α,β-unsaturated aldehydes. These catalysts gave cycloaddition products with high yield, diastereoselectivity, and enantioselectivity (Figure 24.39). Brine was an effective media in the same reaction but promoted by cyclic sulfonyl hydrazine (**123**, 20 mol%) with trichloroacetic acid (TCA, 10 mol%) as co-catalyst, which afforded efficiently the products in good to high yields with high *endo* enantioselectivity [147]. Analogously, aziridin-2-ylmethanol **124**·HClO$_4$ was able to catalyze the same [4+2] cycloaddition reaction of cinnamaldehyde [148].

On the other hand, modified-imidazolidinones endowed with imidazole (**125**) [149] or a fluorous tag in the side chain (**126**) [150] proved to be active in the Diels–Alder cycloaddition in the presence of 5 vol.% water (Figure 24.40). The highly efficient organocatalyst **127** promoted, in the presence of *p*-(trifluoromethyl) benzoic acid, the asymmetric Diels–Alder reaction of cyclohexenones with aromatic nitroolefins in seawater and brine with excellent chemo-, regio-, and stereoselectivities [151]. It has been postulated that the cyclization was involved in a concerted addition process and that seawater and brine significantly promoted the

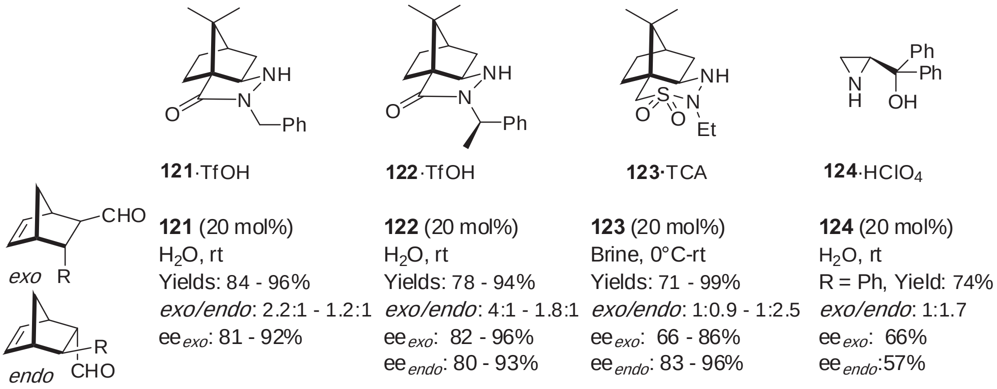


Figure 24.39 Structure of catalysts **121–124** and their catalytic activity in the Diels–Alder reaction.

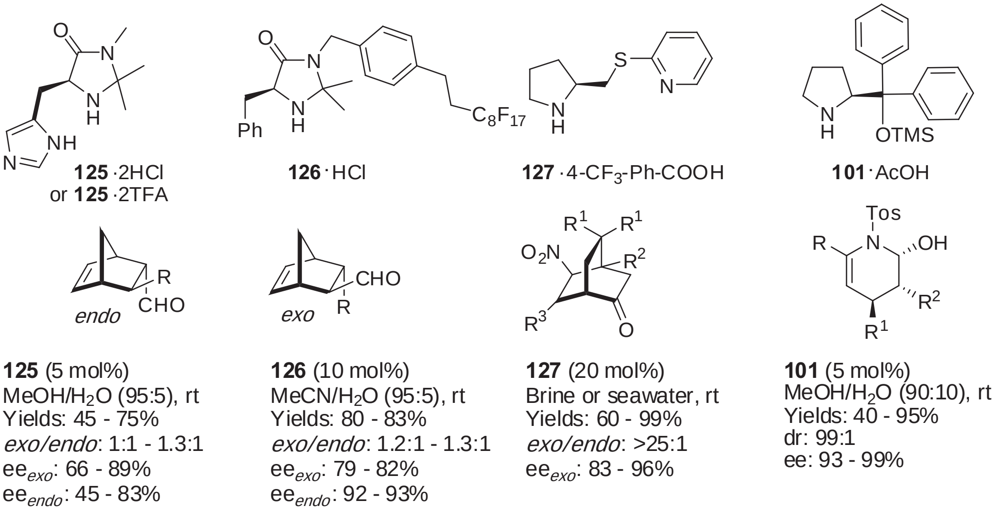
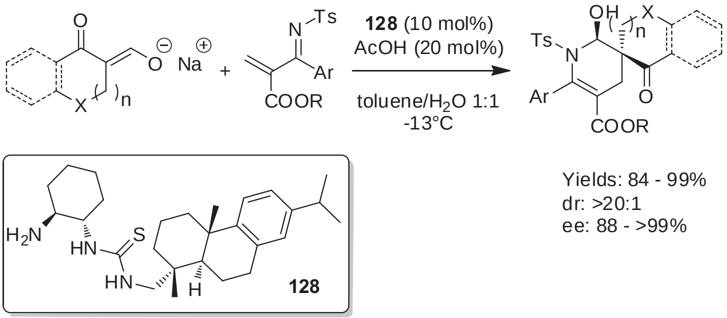


Figure 24.40 Structure of catalysts **125–127** and **101** and their catalytic activity in the Diels–Alder reaction.

reaction, leading both to the same results. The highly stereoselective inverse-electron demand aza-Diels–Alder reactions of substituted *N*-sulfonyl-1-aza-1,3-butadienes and aldehydes were catalyzed by α,α-diphenylprolinol derivative **101** [152]. Water dramatically accelerated the reaction, which took place with excellent enantioselectivities (up to 99% ee) for a broad substrate scope under mild conditions.

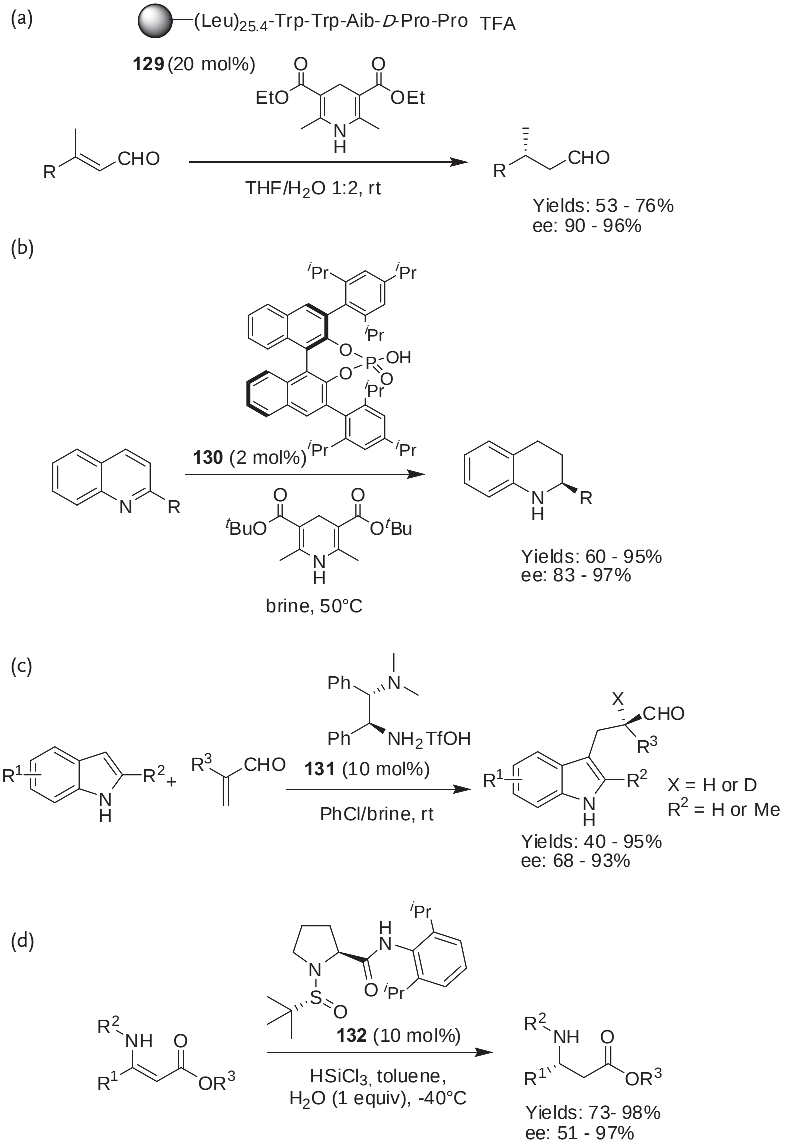
Bifunctional Lewis base organocatalyst **128** proved to be active in the simultaneous activation of the HOMO of the dienophile and the LUMO of the diene in the asymmetric inverse-electron demand Diels–Alder reaction (Scheme 24.6) [153]. In this way, the construction of highly functionalized chiral spirocyclic skeletons with all-carbon quaternary stereocenters can be easily achieved, representing a new method for the synthesis of chiral spirohemiaminals starting from substituted *N*-tosyl-2-methylenebut-3-enoates and cyclic keto/enolate salts. The biphasic solvent mixture of toluene and water was the best reaction media.



Scheme 24.6 Asymmetric inverse-electron demand Diels–Alder reaction promoted by bifunctional catalyst **128**.

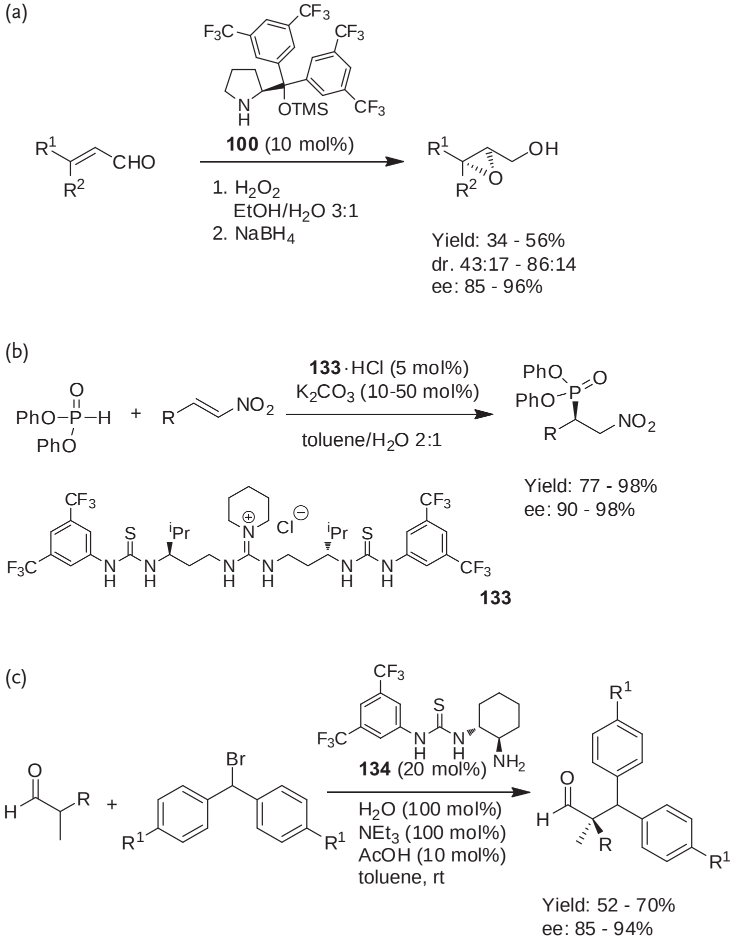
24.6
Miscellaneous Examples

Enantioselective protonation represents one of the most straightforward approaches used by Nature and synthetic chemistry to introduce chiral centers [154]. In recent years several examples regarding different classes of organocatalysts dealing with asymmetric reduction in the presence of water have been reported. A resin-supported *N*-terminal prolyl peptide having a β-turn motif and hydrophobic polyleucine chain (**129**) was able to promote the asymmetric transfer hydrogenation of α,β-unsaturated aldehydes under aqueous conditions (Scheme 24.7a) [155]. The hydrophobic cavity of the polyleucine tether in the aqueous media was responsible for the remarkable acceleration of the reaction as well as for its selectivity. On the other hand, the asymmetric reduction of quinolines by using just 2 mol% of the Brønsted acid catalyst **130** has been achieved recently (Scheme 24.7b) [156]. For the first time such class of catalysts has been employed in aqueous media, displaying good to high yields and selectivities. More recently, the first asymmetric Friedel–Crafts reaction of α-substituted acroleins with indoles and 2-methylindoles have been described, involving tandem C–C bond formation and enantioselective protonation of the enamine intermediate at the α position mediated by **131** (Scheme 24.7c) [157]. In this case, water not only acted as the proton donor, but also enhanced the enantioselectivity of the whole process. Finally, the enantioselective reduction of *N*-alkyl β-enamino esters with trichlorosilane promoted by **132** in the presence of 1 equivalent of water has been reported, with the presence of water being crucial both for the reactivity and selectivity (Scheme 24.7d) [158].



Scheme 24.7 Organocatalyzed protonation reactions carried out in, or in the presence of, water.

The practical application of water as reaction media has been exploited in other asymmetric processes. Indeed, ethanol/water has been the solvent of choice for carrying out the epoxidation of α,β-unsaturated aldehydes employing 2-[bis(3,5-trifluoromethylphenyl)-trimethylsilanyloxy-methyl]pyrrolidine **100** as catalyst (Scheme 24.8a) [159]. Fair to good selectivity has been achieved by using hydrogen peroxide as the oxidant. On the other hand, the enantioselective phospha-Michael addition of diphenyl phosphonate to nitroolefins can be achieved in the presence of water (Scheme 24.8b) [160]. The use of conformationally flexible guanidinium/bis-thiourea organocatalyst **133** afforded excellent yields and selectivities, and proved that the guanidinium cation plays a key role in enhancement of the reaction rate under biphasic conditions in the presence of water, suggesting that the P–C bond-forming reaction might take place through the interaction of guanidinium/phosphite at the interfacial layer. Finally, the primary aminothiourea catalyst **134** is able to catalyze enantioselective alkylation of (*R*)-aryl propionaldehydes with diarylbromomethane in the presence of water (Scheme 24.8c) [161]. Interestingly, several pieces of evidence indicated that a stepwise S_N1 mechanism in the substitution reaction induced by anion binding to the catalyst is involved in the process.



Scheme 24.8 Organocatalyzed miscellaneous reactions in water media.

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Part I
Alpha-Alkylation and Heteroatom Functionalization

25

S_N2-Type Alpha-Alkylation and Allylation Reactions

Christine Tran and Peter I. Dalko

25.1

S_N2-Type Alkylation under Homogenous Conditions

As preformed metal enolates are used as nucleophiles in alkylation reactions [1] the idea of replacing metal enolates with catalytically generated chiral onium enolates or enamines [2, 3] appears straightforward. The challenge in adopting an enantiocatalytic protocol in this transformation is to find conditions for the synthesis of so-called unstabilized enolates in an environment where the nucleophile catalyst may efficiently compete for the same substrate. An S_N2-type organocatalytic alkylation can be realized under phase-transfer conditions, where the onium enolate reacts with selected electrophiles, such as alkyl halides or aldehydes in the organic phase. These reactions are discussed in more detail in Chapter 14. The range of S_N2-type reactions under homogenous conditions is considerably more restricted. The first enantiocatalytic direct S_N2-type α-alkylation of haloaldehydes under homogenous conditions was described under intramolecular conditions by using α-methylproline as catalyst (Scheme 25.1) [4]. The reaction offered cyclopentanes and cyclopropanes in high ee (86–96% ee) and yields (70–94%) with X = I, Br leaving groups and in apolar aprotic solvents, such as $CHCl_3$ or in mesitylene, which also improved the enantioselectivity up to 97% ee.

The transition state (TS) of the transformation was postulated to be analogous to that of proline-mediated enamine reactions, including formation of the (*E*)-enamine [NB: the 1,3-allylic strain disfavors formation of the (*Z*)-conformer] with the rate-determining step of intramolecular nucleophile substitution of the enamine intermediate. The mechanism was also validated by density functional analysis [4b]. It was suggested that the triethylammonium carboxylate might be involved in the activation of the leaving group: in this model, the carboxylic acid proton is transferred to the base, which stays linked to the carboxylate by a strong hydrogen bond, thus providing an electrostatic stabilization of the negative charge of the leaving halide during the S_N2 process (Scheme 25.1). The presence of the base (triethylamine, TEA) might enhance the reaction rate by lowering the activation barrier and influence the stereoselectivity by stabilizing the transition state. According to the suggested TS model the α-methyl substituent of the catalyst **3** is

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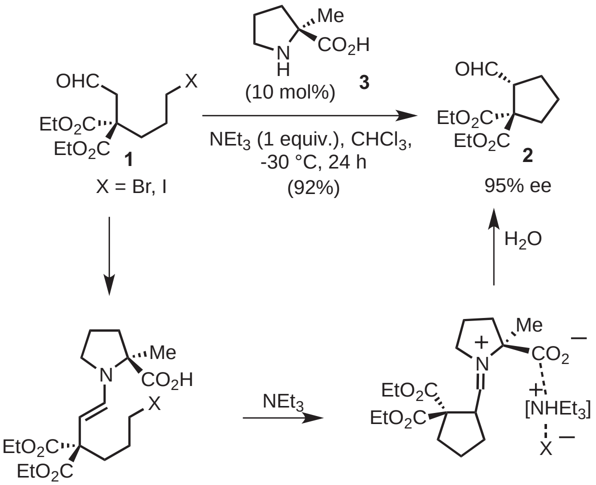


Scheme 25.1 Direct enantiocatalytic *S*$_N$2-type α-alkylation of haloaldehydes.

also a stereo-controlling element: the 2-methylproline catalyst (**3**) gives rise to a more distorted TS than the proline catalyst due to steric interaction between the vinyl and carboxylate groups.

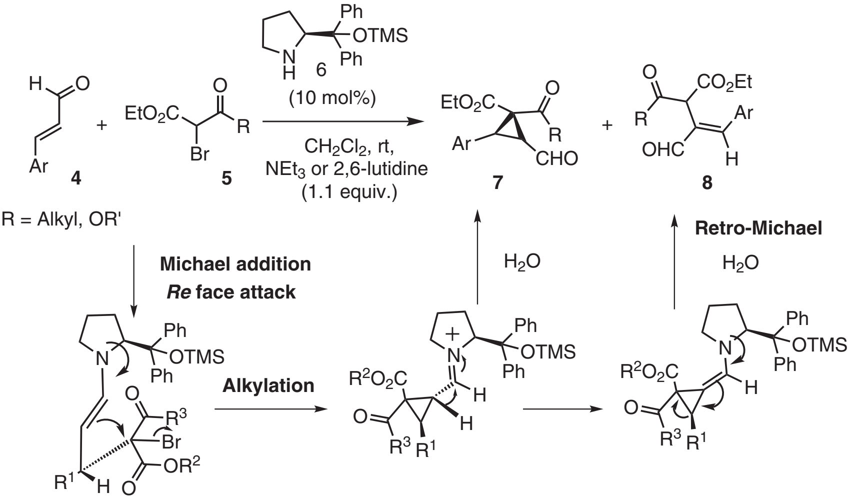
Although this alkylation is efficient under intramolecular conditions, the method performed poorly under intermolecular conditions due to the number of side reactions (racemization) and deactivation of the nucleophile catalyst by alkylation. The reaction was used nevertheless under modified conditions when the 2-methylproline catalyst was replaced by diarylprolinol silyl ether in domino transformations as the final step in alkylation–cyclization reactions [5]. While domino reactions are discussed more in detail in Chapter 37 (see also Chapters 42 and 43), some relevant examples will be discussed here.

25.2
Domino Reactions Including *S*$_N$2-Type Alkylations

Organocatalytic asymmetric domino transformations combining a Michael addition and an aldehyde α-alkylation were developed for the synthesis of enantioenriched cyclopropane and cyclopentane derivatives. Almost simultaneously the Wang [5a] and Córdova groups [5b–d] reported the construction of 2,3,4-trisubstituted cyclopropanes through a Michael/α-alkylation domino reaction, with the halide on the donor, that was also extended recently to "non-stabilized" alkyl halides for inter- or intramolecular α-alkylation reactions of aldehydes [5e]. The Enders group reported the formation of 1,1,2-trisubstituted cyclopentanes by a domino reaction between aliphatic aldehydes and (*E*)-5-iodo-1-nitropent-1-ene [6], adding the halide on the acceptor. These two approaches, that is, halogen on the donor reagent (i) and halogen on the Michael acceptor (ii) remained the two archetypal transformations of the tandem Michael addition/alkylation approach.

25.2.1
Michael/S_N2 Reactions with the Halide on the Donor

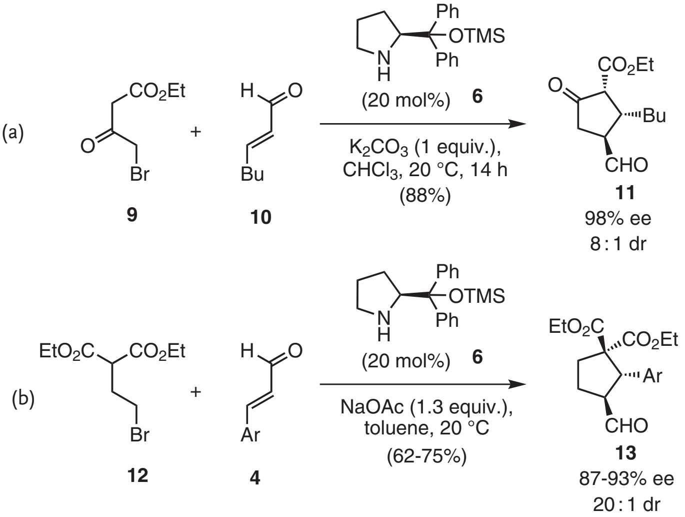
Historically the first cascade Michael–alkylation reaction was described almost simultaneously by the Wang and the Cordova groups by using α,β-unsaturated aldehydes with bromomalonates or bromoacetoacetates. The reaction afforded cyclopropanes or cyclopentenones depending on the position of the halogen and was catalyzed by diphenylprolinol TMS ether (**6**) (Scheme 25.2) [5a,b]. The absence of deactivation of the catalyst by N-alkylation was attributed to the presence of the more abundant enol form of bromomalonates or bromoacetoacetates, (NB: the vinyl bromide is less reactive in alkylation). The reaction offered products in high yield and stereoselectivity (up to 92% ee, dr > 30 : 1, product : by-product ratio: 17 : 1) (Scheme 25.2). Less polar halogenated solvents such as CH_2Cl_2 or $Cl(CH_2)_2Cl$ provided good yields as well as enantio- and diastereoselectivities (yield 88–93%, 91–92% ee, dr > 30 : 1) and resulted in less by-products; nevertheless high diastereoselectivity was observed in CH_3CN and EtOH (dr > 30 : 1) while no reaction occurred in DMF. Acid scavengers such as TEA or 2,6-lutidine afforded the cyclopropane products in high yield (up to 90%) and enantioselectivity (up to 91% ee); a spontaneous ring-opening of cyclopropanes leading to stereoselective (*E*)-α-substituted malonate α,β-unsaturated aldehyde by-product was observed with an excess of NaOAc (93% yield, ratio product:



Scheme 25.2 Enantioselective cascade Michael–alkylation reactions and the postulated mechanism.

by-product: 1 : 3). The enantioselectivity of the reaction was explained by the efficient shielding of the *Si* face of the chiral iminium intermediate by the bulky aryl groups of the catalyst (Scheme 25.2).

The reaction was extended to the synthesis of cyclopentane derivatives by moving the leaving group to position 4 of the acetoacetate ester (Scheme 25.3a) [5c,d]. Bromine was selected as leaving group since the 4-chloro derivative afforded only the Michael addition. More recently the reaction was extended to "non-stabilized" alkyl halides (Scheme 25.3b) [5e]. Somewhat surprisingly no O- or N-alkylation by-products were observed despite the fact that **12** cannot be stabilized by the formation of vinyl halides by enolization, such as in 2-haloethyl-malonates (**9**) (Scheme 25.3a).

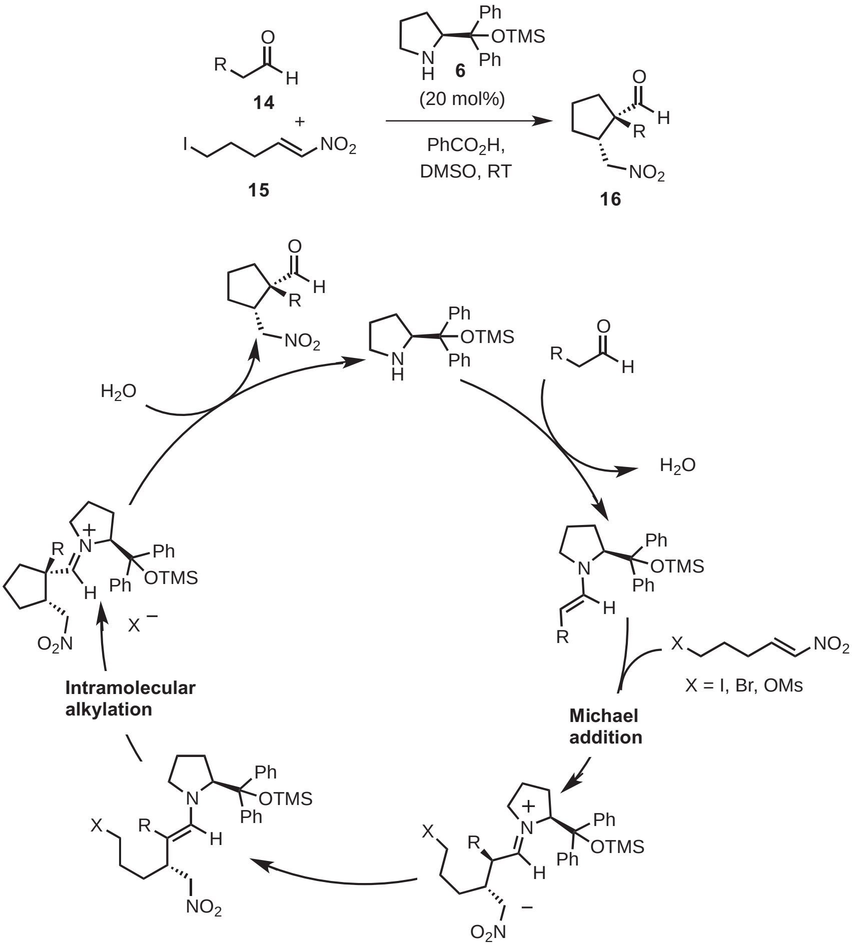


Scheme 25.3 Michael–alkylation reactions with (a) "stabilized" and (b) "non-stabilized" alkyl halides.

25.2.2
Michael/S_N2 Reactions with the Halide on the Acceptor

Taking advantage of the usually high enantioselectivity of the addition of diphenylprolinol silyl enamines to nitroolefins the Enders group developed a large palette of domino sequences [7], including Michael/S_N2 tandems in the presence of aliphatic aldehydes and the ω-iodonitroalkenes [5f]. Cyclopentanes were obtained, albeit in a low chemical yield and diastereoselectivity (20%, 70 : 30 dr) but with excellent enantioselectivity (*trans*: 94% ee, *cis*: 95% ee). The presence of benzoic acid co-catalyst increased both chemical yield and enantioselectivity

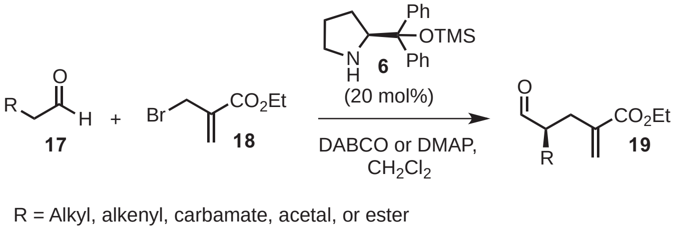
(62% yield; *trans:* 94% ee, *cis:* 96% ee). Notably, bromo and mesylate derivatives afforded exclusively the Michael product (70–80%). Less polar solvents such as THF or CH_2Cl_2 favored the formation of the Michael adduct likewise, while polar solvents such as DMF or DMSO increased the yield of the domino product up to 55%. The key enantiodifferentiating step of the transformation is the highly enantioselective Michael addition of the transiently formed enamine in the presence of the TMS diphenylprolinol catalyst at the more accessible *Si* face of the TMS-prolinol enamine. The cyclopentane product is formed by an intramolecular nucleophile substitution reaction from the *Re* face at C(α) of the enamine (Scheme 25.4).



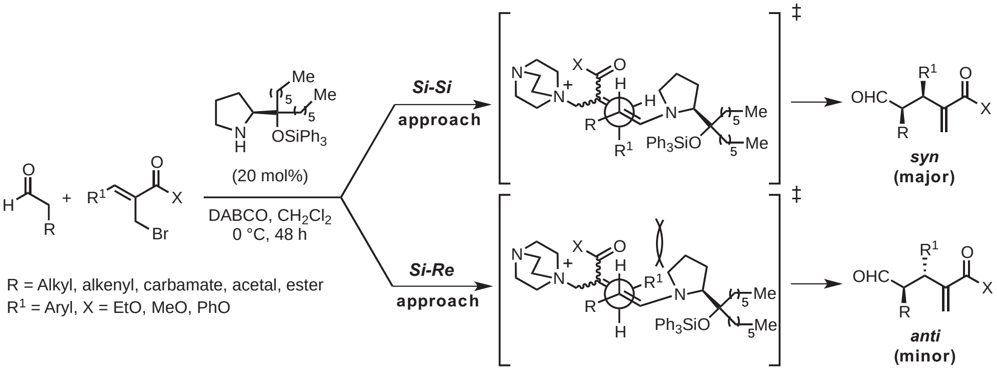
Scheme 25.4 Organocatalytic domino Michael addition/alkylation reaction and plausible catalytic cycle of the domino sequence.

25.3
Intermolecular S_N2' Alkylations under Homogenous Conditions

Intermolecular α-alkylation of aldehydes with 2-(bromomethyl)acrylates **18** were developed by the Palomo group [8]. The reaction was best catalyzed by diphenylprolinol TMS (**6**)(Scheme 25.5) or dihexylprolinol triphenylsilyl ethers (Scheme 25.6), and required the presence of an acid scavenger, such as DABCO or DMAP.



Scheme 25.5 Enantioselective α-alkylation of aldehydes with 2-(bromomethyl)acrylates.



Scheme 25.6 Postulated mechanism and TS of the α-alkylation of aldehydes with 2-(bromomethyl)acrylates.

The reaction is general for various acrylates having or not substituents at the γ-position (R^1 = Aryl, CO_2Me) and aldehydes (R = alkyl, alkenyl, carbamate, acetal, ester), (yield: 50–87%, ee: 87–98%, *syn*:*anti*: 80:20–94:6). By using chiral aldehydes such as (*S*)-citronellal, the reaction presented high diastereoselectivity (97:3 dr) for the matched pair.

To rationalize the sequence a S_N2' mechanism was suggested, leading to an ammonium salt (NB: the DFT computed S_N2 pathway involved considerably higher TS energy). Subsequently, an addition–elimination step was suggested for the formation of the aldehyde end-product (Scheme 25.6). The diastereoselectivity might be the consequence of an open transition state with an (*E*)/*s-trans* enamine configuration, which is also regarded as the most stable, in which a *Si–Si* approach with minimized *gauche* interactions is the most favorable (Scheme 25.6).

25.4
Summary

S_N2-type organocatalytic alkylations have been developed under intramolecular conditions, leading to chiral cyclopropanes and cyclopentane derivatives under intramolecular conditions and were used in domino transformations as the final step. S_N2-type alkylations with phase-transfer alkylations (Chapter 14), S_N1-type reactions (Chapter 26), and free radical and electron-transfer SOMO-alkylations (Chapter 39) are gaining increasing importance in the organocatalytic arsenal.

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26

Alpha-Alkylation by S_N1-Type Reactions

Andrea Gualandi, Diego Petruzziello, Enrico Emer, and Pier Giorgio Cozzi

26.1

Introduction

Rediscovering and inventing new chemistry by a more suitable use of natural resources and feedstock is becoming an important issue nowadays. Creativity is one of the arm in the arsenal of chemists in response to the enormous challenges posed by limited resources, increasing cost of energy, and pollution. The development of green chemistry and green engineering in the pharmaceutical industry was encouraged by several political parties and government policy. In the list of priority key research areas, the development of new nucleophilic substitution reactions of alcohols is frequently encountered, as this transformation is frequently used for the preparation of active pharmaceutical ingredients. However, to realize this key reaction alcohols are transformed into the more reactive halides or sulfonate esters to permit their reaction with nucleophiles. The activation reaction and the successive transformation produce waste. A greener and more suitable approach is certainly the direct nucleophilic substitution of an alcohol since one of the by-products from the reaction is water. Many catalytically and practical methodologies have appeared in recent years that are able to overcome the reluctance of the hydroxide ion, a poor leaving group, towards the reaction. Recently, the direct substitution of allylic, benzylic, and tertiary alcohols has been achieved via an S_N1-type reaction with a catalytic amount of Brønsted or Lewis acids [1]. When a new stereogenic center is formed, most of these transformations produce the desired product in racemic form, as carbenium ions are involved [2]. Although diastereoselective addition to a prostereogenic carbenium ion, generated by suitable precursors, was described recently, stereoselective processes involving an S_N1-type of reaction were still an unexplored research area. The arsenal of activation modes available in organocatalysis [3] can be used to set up suitable reaction conditions in which chiral nucleophiles (enamine catalysis) or chiral electrophiles (iminium catalysis, chiral counter-ion catalysis) can be easily generated (Figure 26.1). The use of organocatalytic stereoselective S_N1-type reactions was recently described. A general overview of recent results in this developing area and all the new directions opened up are presented here, along with the most recent results in this new research area.

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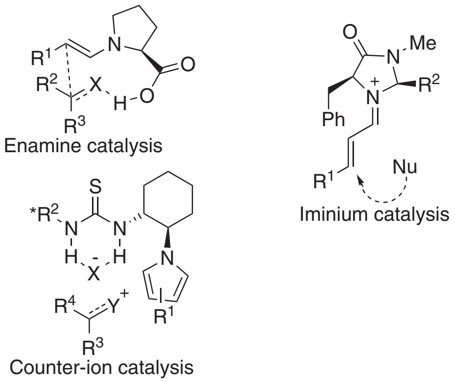


Enamine catalysis

Counter-ion catalysis

Iminium catalysis

Figure 26.1 Activation modes in organocatalysis.

26.2
S_N1-Type Nucleophilic Reaction by Generation of Carbocations

The key-steps in many organocatalytic cycles are electrophile–nucleophile combinations. The reactions of carbocations and Michael acceptors with C, N, O, and P nucleophiles were carefully studied by Mayr, providing an empirical equation able to describe the reaction rates [4].

Nucleophile and electrophile combinations are reported to follow Eq. (26.1) [5], where electrophiles are characterized by one parameter (electrophilicity E) and nucleophiles are characterized by two parameters (slope s_N and nucleophilicity N):

$$\log k_{20\,°\mathrm{C}} = s_{\mathrm{N}}(N + E) \qquad (26.1)$$

The parameters E and N can be used to compare the reactivity of compounds and even to predict the possibility that a reaction occurs. The parameter E represents the electrophilicity parameter, which is defined by the use of a reference electrophilic compound. The values of E for many carbenium ions have been determined [6]. Contrary to common sense, which considers the carbenium ion to be intractable, it is possible to classify several carbenium ions that differ in electrophilicity by more than 16 orders of magnitude. Their stability is strictly connected to the presence of aryl, alkenyl, or alkynyl groups directly connected to the carbenium ionic center. For these reasons, sometimes the phrase "π activated alcohol" [7] is encountered for this type of compounds. The tables compiled by Mayr (Figure 26.2) offers a more readable and precise definition for the stability and reactivity of carbenium ions. Carbenium compounds with $E < 0$ (benzhydrylium ion) are almost impossible to isolate and to store without their rapid decomposition [8].

Several S_N1-type reactions can be now rationally designed through the use of the Mayr scales of reactivity [9]. To design a new reaction of carbocations it is quite

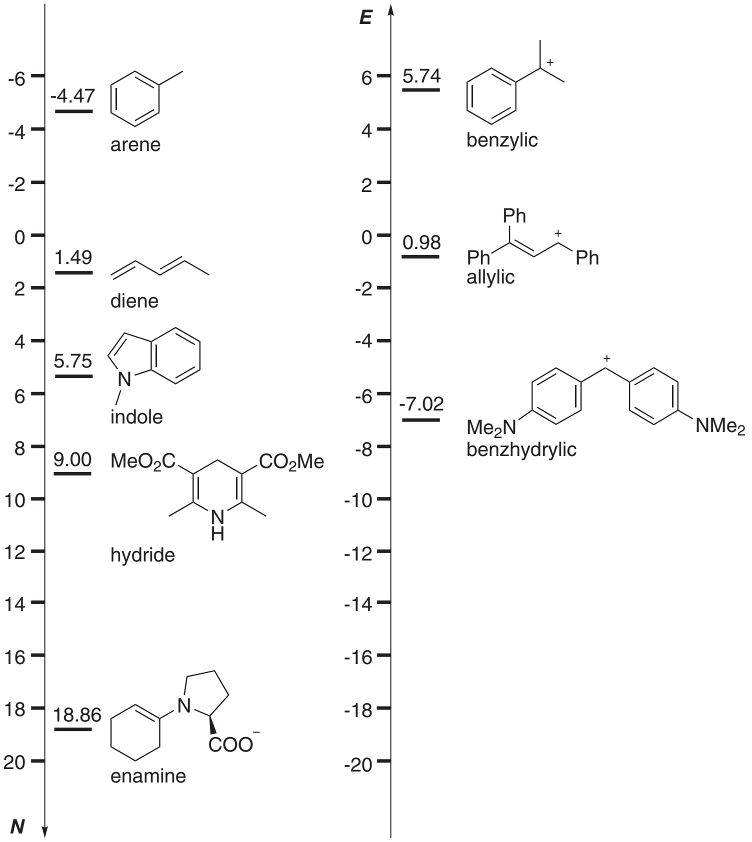


Figure 26.2 Mayr's table of reactivity.

important to consider both the electrophile and the nucleophile together. Mayr has in fact established a predictive "rules of thumb" [10] for determining if a reaction between an electrophile and a nucleophile will be successful, neglecting the limitations arising from steric effects [11]. In addition, as mentioned, the nucleophilic character of the solvent needs to be taken into consideration, because it can compete with the nucleophilicity of other reagents [12].

As isolated carbenium ions are difficult to handle, these S_N1-type of reactions can be quite limited in scope. However, benzylic, propargylic, and allylic alcohols can form, in the presence of Lewis or Brønsted acids, a carbenium ion, providing the sources of suitable electrophilic partners. In general, strong electron-donating substituents enhance the stability of carbenium ions, and carbenium ions located at –7 of the Mayr scale are air and bench stable for months [13]. Benzylic carbocations are, vice versa, of moderate stability and high reactivity, and therefore can react with a large variety of possible nucleophiles. Propargylic carbocations are positioned close to 0 on the Mayr scale; the coordination of the triple bond fragment with $Co(CO)_6$ lowers the electrophilicity of the carbocation. The reaction of propargylic cation (S_N1-type Nicholas reactions) with enamine was described by Mayr [14] and can be readily interpreted by the Mayr table of reactivity. Allylic cations, formed from suitable precursors (alcohols or halides), are another type intermediates active in S_N1-type reactions. In some cases, electrofugality concepts [15], again developed by Mayr, are useful for allowing the controlled generation of stable cationic substrates, particularly when hydrogen bond catalysts are employed. Finally, chiral Brønsted acids can generate cationic intermediates forming a chiral counter ion, which is able to control the approach of a nucleophile [16]. Mayr has recently started to introduce quantitative measures for electrophilicity and nucleophilicity in the organocatalytic field by including the iminium [17], and other organocatalytic intermediates [18], in the context of the Mayr scale. Note that the possibility of using an S_N1-type reaction in organocatalysis is strictly connected to the presence of water in the reaction medium, or due to the catalytic cycle (Figure 26.3).

Water is a nucleophile and is at a precise position on the Mayr scale [12]; the presence of water can compete in an S_N1-type reaction, hampering the nucleophilic addition of substrates. In addition, the formation of highly electrophilic cationic intermediates can induce its reaction with the precursor, in particular this problem is often observed when alcohols are used as precursor in S_N1-type reactions [19].

However, the scope of organocatalytic reactions has increased in recent years through the formation of reactive intermediates generated in the presence of nucleophiles by the action of synergistic catalysis [20]. This is a powerful synthetic strategy for new reaction development that allows us to combine organometallic chemistry and organocatalytic concepts.

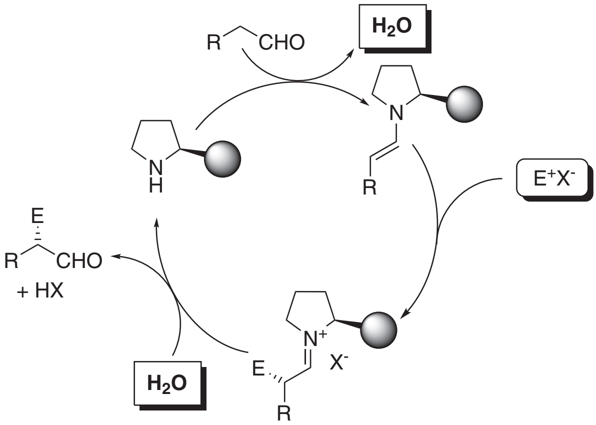


Figure 26.3 Catalytic cycle involved in organocatalytic processes mediated by enamine catalysis.

26.3
Organocatalytic Stereoselective S_N1-Type Reactions with Enamine Catalysis

In most direct substitution reactions of alcohols with nucleophiles, in which a carbocation is presumably generated, the stereochemical information of enantioenriched starting material is completely lost during the process. However, chiral carbocations of highly stability (e.g., the 1,13-dimethoxyquinacridinium cation) can be obtained in highly enantioenriched form [21]. In general, the formation of a carbenium intermediate poses a severe challenge for enantioselective transformations. The challenge can be addressed by the use of a chiral nucleophile, or by the use of a chiral counter ion. When the nucleophilic compound is entering a transient chiral state, the carbenium ion can be approached only by one face of the attaching chiral nucleophiles. Recently, this concept was exploited in organocatalysis by the transient formation of chiral enamines that acted as powerful nucleophiles [22]. Several secondary and primary amines were introduced as catalysts in this field, but the reaction of the corresponding enamines with carbocations was rarely explored. Enders [23] and Melchiorre and Petrini [24] have hypothesized the formation of highly stable carbocations A and B fragments from the indolic framework (Figure 26.4). The *in situ* formation of such a hypothetical carbocation occurs from a stable precursor, and an S_N1-type reaction involving the carbocation and enamine leads to a “formal” α-alkylation. The resultant cation was shown to exist as either a vinylogous iminium cation or a carbenium ion by DFT calculations [25]. The positive charge is delocalized and distributed over the conjugate system, and thus the vinylogous iminium cation is more likely to be involved.

In particular, Enders selected indoles and *N*-tosyliminoenoates **1** as the nucleophilic and electrophilic components, respectively, for this reaction (Figure 26.4).

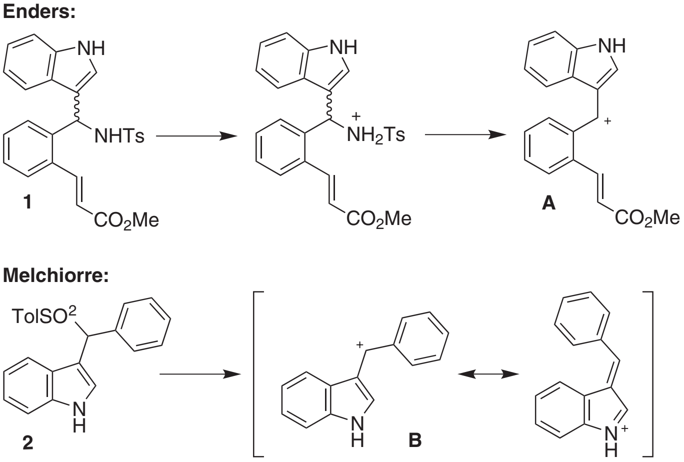
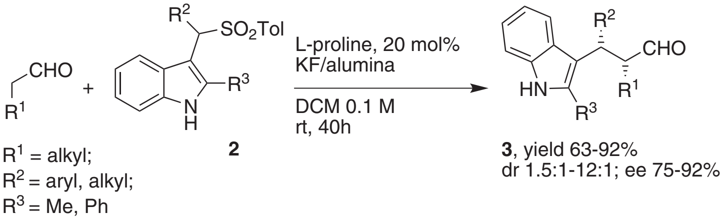


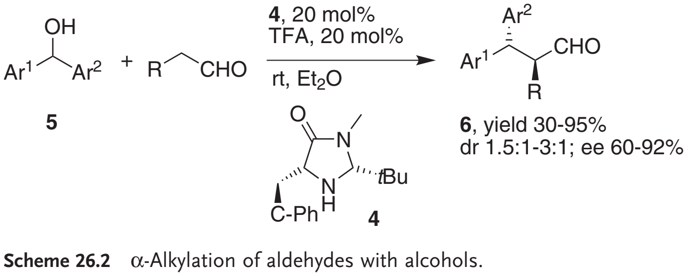
Figure 26.4 Transient carbenium ion formation from an indolic framework.

The more acidic BINOL-derived phosphoric acids *N*-triflyl phosphoramides, active in many reactions [26], were prepared and found able to catalyze the Friedel–Crafts reaction. When the reaction was stopped prior to completion, the enantiomerically enriched adduct was isolated (66 ee%). Accordingly, a reasonable mechanistic proposed assumes a rapid and reversible protonation with preferential dissociation of tosylamide ($TsNH_2$) from one of the diastereomeric ions, with formation of the resultant carbenium ion A. Melchiorre recently used the 3-(1-arylsulfonylalkyl) indoles (**2**) as suitable electrophilic precursors for generating carbenium ion B. In fact the sulfonyl moiety at the benzylic position of 3-substituted indoles is a good leaving group. The vinylogous cation was generated with KF on alumina in the presence of L-proline (20 mol%) to provide the desired catalytic activity, leading with aldehydes to the formation of alkylated product **3** with good stereoselection (Scheme 26.1).



Scheme 26.1 Proline-catalyzed alkylation of arylsulfonyl indoles.

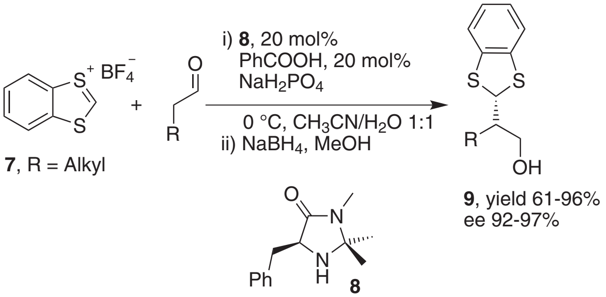
Notably, proline was unique for this transformation, as all the other chiral secondary amines tested failed to promote the reaction. Another well-established organocatalyst (**4**), invented by MacMillan [27], and unable to form secondary interactions with electrophiles like proline, was used in the addition of aldehydes to indolyl and other carbocations derived from alcohols. The formation of stable carbenium ions from alcohols and their compatibility with water, generated by the organocatalytic cycle (formation of enamines from the corresponding carbonyl derivatives), was established by Cozzi in a S_N1 nucleophilic substitution of alcohols in the presence of water [28]. The enamine formed *in situ* by the MacMillan catalyst approaches the carbocation from the less hindered side and the hindrance of the incipient carbocation controls the stereoselectivity of the reaction (Scheme 26.2) [29].



Scheme 26.2 α-Alkylation of aldehydes with alcohols.

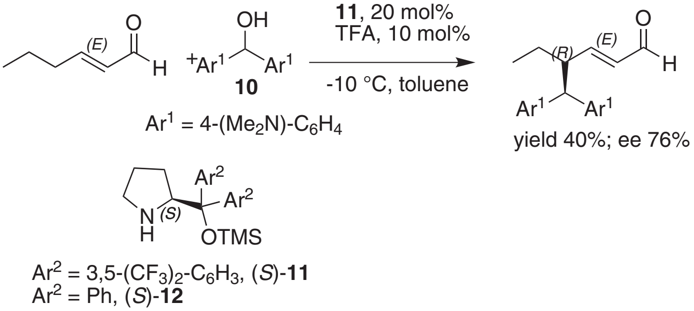
Not only alcohols can be used with the MacMillan catalyst–isolated and stable carbenium ions are also suitable partners for the reaction [30]. Tropylium tetrafluoroborate is commercially available, and it is a stable carbenium ion that can be used in this type of reaction without any precautions. However, other carbenium ions are less stable and are difficult to generate; they can be obtained using the conditions described by Mayr in his papers as unstable solids. Although the application of an S_N1-type reaction with alcohols seems to be limited to the use of the MacMillan catalyst, the Hayashi–Jørgensen catalyst is also suitable for this transformation [31].

The presence of acid additives in organocatalytic process involving aldehydes is crucial to allow formation of the corresponding enamine and for enhancing the rate of the catalytic processes [32]. The stability of the Hayashi catalysts is determined by the acid used as additive. With the more stable MacMillan catalyst, TFA or a stronger acid can be used while, normally, the Hayashi catalyst is used with benzoic acids or other acids with similar pK_a. The Jørgensen catalyst allows instead the use of TFA, *p*-TSA, and triflic acid [31]. Although several significant achievements in the field of the α-alkylation of aldehydes were reported recently, this transformation was considered the "Holy Grail" of organocatalysis [33]. The introduction of a methyl or ethyl chain, though, is not possible by an S_N1 type reaction. Cozzi has recently used the 1,3-benzodithiolylium cation **7** as a practical formyl equivalent in an organocatalytic general approach to the alkylation of aldehydes (Scheme 26.3) [34].



Scheme 26.3 Alkylation of aldehydes with benzodithiolylium ion.

The introduction of a 1,3-benzodithiol group in a stereoselective fashion can be used to generate an anionic or cationic equivalent and could be easy removed by Raney nickel. This procedure was applied to the synthesis arundic acid [34], which is currently undergoing phase II development for the treatment of acute ischemic stroke, and to the bisabolane skeleton (P. Canestrari, E. Emer, A. Gualandi, and P.G. Cozzi, unpublished results). The procedure was recently extended to the formation of quaternary stereogenic centers, in particular the alkylation of α-branched aldehydes with the benzodithiolylium ion can be catalyzed by the use of 9-amino-9-deoxy-epi-cinchona alkaloid primary amines [35]. The use of primary amine in organocatalysis was exploited by Melchiorre using dienamine catalysis to promote vinylogous nucleophilicity in an $S_\mathrm{N}1$-type reaction. The *γ*-alkylation of linear α-branched enals is catalyzed by a synergic catalyst [36] that integrates dienamine catalysis and Brønsted acid catalysis simultaneously. Melchiorre described the direct γ-alkylation of α-branched aldehydes with bis(4-dimethylaminophenyl)methanol (**10**) [37]. This alcohol can form the corresponding carbenium ion in water, and it is a rather stable carbenium ion positioned at −7 of the Mayr scale. Unsurprisingly, **10** is generally used in most organocatalytic processes, while extension to less stabilized carbenium ions is not common. Several concepts can be envisaged by this organocatalytic activation of enals. The benzylic cation, with a chiral phosphate counter ion, interacts with a dienamine through a network of not-covalent interactions and evidence of the cooperation between the two catalysts is observed with the mismatched combination of the catalysts. Similar results in term of the alkylation of aldehydes were obtained by Herrera and Christmann [38] by use of the Jørgensen α,α-diarylprolinol organocatalyst O-TMS ether (*R*)-**11** without the need of a double activation (Scheme 26.4).



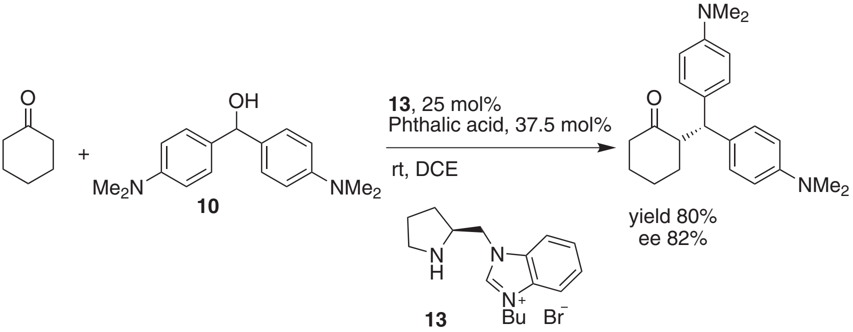
Scheme 26.4 γ-Alkylation promoted by the Jørgensen α,α-diarylprolinol organocatalyst.

However, only linear and β-substituted α,β-unsaturated aldehydes favor the γ-substitution. In many cases a mixture of α and γ products were isolated. In a quite similar manner γ,γ-disubstituted aldehydes can react with 3-indolylmethanols, which clearly represent a privileged structure for $S_\mathrm{N}1$-type reactions. The reaction was promoted by (*S*)-**12** (5 mol%) and AcOH (10 mol%), giving exclusively the α-regioselective alkylation product [39].

Generation of the carbenium ion in an $S_\mathrm{N}1$-type reaction with aldehydes can also be realized in different ways; for example, the carbenium ion can be prepared directly from a CH bond by a formal CH oxidation. The CH bond can be oxidized by electrochemistry methodologies [40] or by the use of oxidants in stoichiometric amount. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been utilized in efficient oxidative coupling reactions involving CH activation. An organocatalytic asymmetric oxidative coupling of benzylic compounds with aldehydes performed with the MacMillan catalysts **4** and DDQ was described [41]. Better enantiomeric excesses with the same substrates could be obtained by the use of oxygen as oxidant [42]. As in both reactions the intermediacy of a carbenium ion was established, the results obtained in terms of stereoselectivity are quite comparable to those obtained with the carbenium ion isolated by alcohols [43].

26.4
Asymmetric S_N1-Type α-Alkylation of Ketones

Despite the advances obtained in the α-alkylation of aldehydes, the intermolecular alkylation of ketones was achieved only very recently. The S_N1-type reaction with ketones was described by Cheng and coworker, using a tagged ionic liquid catalysts **13** (Scheme 26.5) [44].

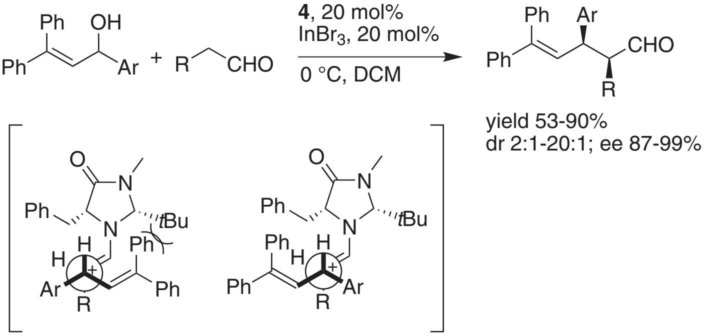


Scheme 26.5 Alkylation of ketones with the benzhydrilic alcohol **10**.

The reaction was performed with cyclic ketones and with alcohols able to form a quite stable carbenium ion ($-7 < E < -5$). Other alcohols giving a more electrophilic carbenium ion were not suitable for the reaction. The tagged catalyst was used in 25 mol% in the presence of phthalic acid as additive. The reaction showed a broad scope to respect the ketone, as 4-substituted cyclohexanones were employed. In most cases the S_N1-type alkylation of 4-substituited cyclohexanone produced just one diastereoisomer in excellent yield and good ee (72–87%). The major diastereoisomer obtained is in agreement with a model in which the steric repulsion between the incoming carbenium ion and the 4-substituent promotes formation of the desired diastereoisomer. The presence of an electrostatic interaction between the carbenium ion and the enamine may contribute to the observed stereocontrol. Noticeably, typical amino-catalysts such as proline, diarylprolinol, and primary amine based on cinchona alkaloids led to low yield and low stereoselectivity. However, these tagged catalysts are used in high loading. Recently, Kokotos described [45] a catalyst based on a chiral pyrrolidine linked to a chiral thiooxotetrahydropyrimidinone that is highly effective for stereoselective alkylation of cyclic ketones in S_N1-type reactions using a low loading of catalyst. The corresponding alkylated products were obtained in quantitative yields and in good stereoselection (up to 80% ee). Unfortunately, the reaction was not general with respect to the alcohols and only alcohols giving a very stable carbenium ion ($E = -7$) can be employed. A broader scope concerning the generation of carbenium ion was obtained by Tian and coworkers [46], who selected benzylic sulfonamides as starting material, following the idea of generating the carbenium ion from other suitable precursors. Through extensive optimization they found that a chiral imidazolidinone substituted with a benzothiophene group gave the product in high stereoselectivity. The aromatic and heteroaromatic moieties introduced in the imidazolidinone are crucial for the formation of iminiums and enamines from ketones [47]. The scope of the reaction is limited to substituted cyclohexanone, as cyclopentanone, tetralone, and cyclooctanone give the desired product with less than 10% ee while cyclic ketones were completely inert. TFA is used as additive and according to the mechanism presented by the authors it is able to cleave the *N*-benzylic sulfonamide into the corresponding carbenium ion. The catalytic cycle of the transformation was supported by ESI-MS (positive mode) spectroscopic analysis of the reaction mixture. Naturally, the scope of S_N1-type α-alkylation of ketones is still narrow and a general solution is still missing. In an attempt to find a general and quite applicable methodology for the alkylation of aldehydes Cozzi and coworkers have investigated the use of the benzodithiolylium ion in the alkylation of ketones. Quite remarkably, general conditions for the alkylation of cyclohexanone were found by the use of the simple amino acid tryptophan as catalyst and up to 75% ee was obtained. However, the fast background reaction, determined by Brønsted acid catalyzed formation of the ketone enol, hampered further improvement of this preliminary result [48].

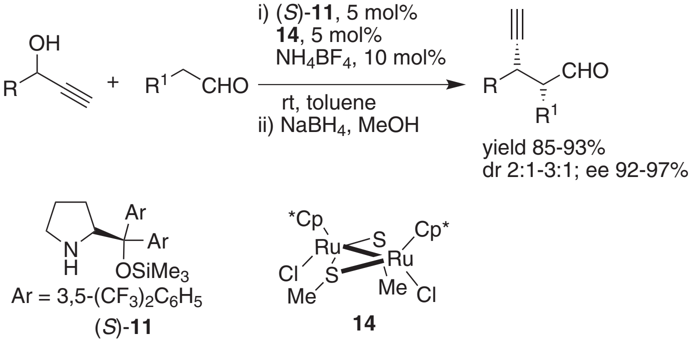
26.5
Combination of Enamine Catalysis and Lewis Acids in S_N1-Type Reactions

As well evidenced by recent reviews [1] S_N1-type direct nucleophilic substitution of alcohols can be promoted by a huge variety of Lewis and Brønsted acids. The carbenium ion can be generated by a catalytic amount of Lewis acid. The synergistic use of Lewis acids and organocatalysts in promoting innovative transformations was reviewed recently [49]. Furthermore, S_N1-type reactions can take advantage of the judicious use of Lewis acids. However, to promote the organocatalytic transformation, the Lewis acid needs to be compatible with water, generated in the catalytic cycle or present in the reaction media, and it needs to be compatible with enamine and secondary amine present in the reaction mixture. Not many Lewis acids have good characteristics for being compatible in such conditions. Kobayashi, in his pioneering studies, has described all the parameters for a good Lewis acid to be compatible in the presence of water [50]. Gold, indium, ruthenium, and copper have been found compatible with organocatalytic processes. In the case of S_N1-type reactions, indium, copper, and ruthenium have been used to achieve good stereoselectivity in quite innovative processes. The combination of organocatalysis with metal catalytic processes was disclosed by Córdova and Ibrahem with the first example of synergy between transition-metal catalysis and aminocatalysis for the direct catalytic intermolecular α-allylic alkylation of aldehydes and cyclic ketones [51]. However, the stereoselective process was achieved only by a metal-catalyzed reaction. Recently, the reaction was re-explored by Breit and coworkers in a dual Pd/proline-catalyzed α-allylation of aldehydes with alcohols [52], but also in this case no enantiomeric excess was recorded. Notably, palladium allyl complexes are moderately electrophilic and quite stable (positioned at −14 on the Mayr scale) and can be generated from the corresponding alcohols. Very recently, Ibrahem and Córdova [53] were able to solve the problem related to the direct intermolecular regiospecific and highly enantioselective α-allylic alkylation of linear aldehydes, by combining the achiral bench-stable $Pd(PPh_3)_4$ complexes with α,α-diphenylprolinol O-TMS ether. To avoid racemization of the compound, which was probably the major problem in previous studies, the products were reduced at −20 °C with $NaBH_4$ before isolation. A combination of DMSO/DMF was found to give the highest tradeoff between reactivity and enantioselectivity. The complete elimination of traces of oxygen seems not to be important in this chemistry, although the reaction needs to be performed, contrary to other S_N1-type reactions, under nitrogen atmosphere. The corresponding 2-alkyl alcohols were isolated in high yields with high enantiomeric ratios (up to 96% ee) and the methodology was applied to the concise total syntheses of biologically active natural products. The reaction with an allyl carbenium ion can be performed without generating the palladium allyl electrophiles. In the approach established by Cozzi the allylic carbenium ion is generated in the presence of the organocatalyst developed by MacMillan (**4**) and $InBr_3$ as a co-catalyst [54] (Scheme 26.6).



Scheme 26.6 Organocatalytic stereoselective alkylation of allylic alcohols with aldehydes in the presence of $InBr_3$.

$InBr_3$ and other indium salts can generate the corresponding ether from the alcohol, and the carbenium ion is then slowly released in the reaction mixture, where it reacts in an irreversible manner with the chiral enamine formed *in situ*. The compatibility of indium salts with organocatalytic process is dictated by the fact that indium is able to mediate several organic transformations, in the presence of water, and the indium salts are not deactivated by water even when it is present in large excess. In addition, the fast dynamic exchange between indium and basic amine nucleophiles, allows the process catalyzed by a Lewis acid to occur. Contrary to other S_N1-type reactions, the use of Hayashi–Jørgensen catalysts (**11**, **12**) is not possible in the presence of indium. Since the hindrance of the allylic carbenium ion controls the dr of the reaction, the dr was increased by considering the more hindered 1,1,3-triphenylallyl carbenium ion. The major *syn* stereoisomer was obtained, caused by hindrance of the diphenyl substituent with the *t*-butyl substituent of the enamine (Scheme 26.6). The compatibility of indium with the organocatalytic stereoselective process was also extended to promote the enantioselective propargylic alkylation of internal alkynes. The facile, catalytic, and highly stereoselective organocatalytic alkylation of internal propargylic alcohols with aldehydes in the presence of water as reaction solvent and a MacMillan catalyst was reported [55a]. It is quite remarkable that the S_N1-type reaction is not blocked by water and that the reaction works only in the presence of indium salts. Water controls the tendency of the propargylic carbenium ion to form the corresponding ether. The possibility of establishing a S_N1-type reaction of a propargylic cation in water is dictated by the carbocation stability relative to the nucleophilicity of water. The substrates able to undergo the propargylation were selected on the basis of the Mayr parameters. The presence of a *p*-NMe_2 group on the aromatic ring is able to enhance considerably the stability of the carbenium ion and many substrates containing this activating group were selected. The advantage of the dimethylamino functionality is further enhanced by the possibility of using nickel- and palladium-catalyzed substitutions of the corresponding salts, as already reported by MacMillan in the context of a total synthesis [56]. The propargylation reaction tolerates a range of functional groups, including thioethers, amides, silyl ethers, and even acetals. The absolute and relative configurations of the products obtained in the reaction are generally in agreement with the general model of an S_N1-type reaction between a hindered carbenium ion and an enamine formed with the MacMillan catalyst. Nishibayashi has described the same organocatalytic reaction using indium salts and CH_2Cl_2 as reaction solvent where the propargylic alcohols were activated by the presence of one or more methoxy substituents on aromatic ring [57]. Slightly lower drs were obtained in the described reaction conditions, highlighting the role of water in determining the selectivity of the process. Interestingly, the cooperative catalytic reactions were also carried out by using $FeCl_3$ instead of $InBr_3$ as Lewis acid. More work is necessary to establish if $FeCl_3$ could be used in other organocatalytic S_N1-type reactions. Cozzi and coworkers have recently extended the use of indium salts in the organocatalytic addition of aldehydes to activated benzylic substrates bearing various functional groups [55b]. Again the presence of the *p*-NMe_2 group in the aryl moiety was mandatory to observe high stereoselection. Quite surprisingly, the reaction gave good drs (up to 15 : 1) and very excellent ees in hexane. The first stereoselective addition of aldehydes to terminal propargylic alcohols was described by Nishibayashi [58]. This study is remarkable because it enhances the compatibility of the S_N1-type reaction with ruthenium complexes. In addition, the possibility of using enamine catalysis and forming in a simple manner chiral nucleophiles increases interest in this chemistry, as the enamines generated *in situ* from aldehydes enantioselectively attack the ruthenium–allenylidene complexes. The presence of both transition metal catalyst (ruthenium complex) and organocatalyst (secondary amine) is crucial and they work cooperatively to promote the reaction. The thiolate-bridged diruthenium complex **14** enabled the propargylic alkylation of propargylic alcohols with aldehydes in the presence of a catalytic amount of a secondary amine (*S*)-**11** as organocatalyst; the corresponding products were isolated in high yields with an excellent stereoselection (Scheme 26.7).

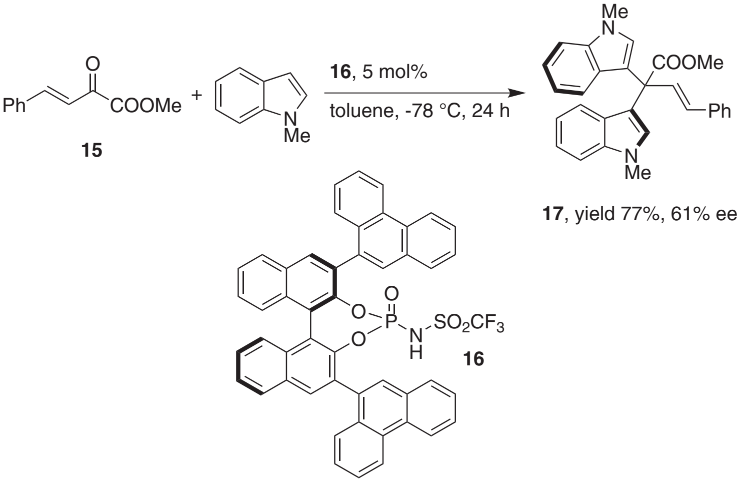


Scheme 26.7 Synergic organocatalytic addition developed by Nishibayashi.

Copper complexes can be also used to activate propargylic esters in the organocatalytic reaction. In the same manner as with ruthenium complexes, the reaction proceeds via a copper-allenylidene complex. The reactions of propargylic esters with aldehydes can be catalyzed by the Hayashi–Jørgensen catalyst, in the presence of a copper complex bearing racemic diphosphine, giving the corresponding propargylic alkylated products in good stereoselectivity [59].

26.6
Organocatalytic S_N1-Type Reactions with Brønsted Acids

One of the first observations on the possibility of performing stereoselective organocatalytic S_N1-type reactions was disclosed by Rueping in 2008 [60]. The reaction of *N*-methylindole with an unsaturated keto-ester **15**, in the presence of catalytic amounts of *N*-triflylphosphoramide **16** as Brønsted acid, gave principally the product of 1,4-addition of indole to the unsaturated compound. However, beside the desired product, an interesting bis indole **17** (Scheme 26.8) was isolated, and the reaction was fully optimized.



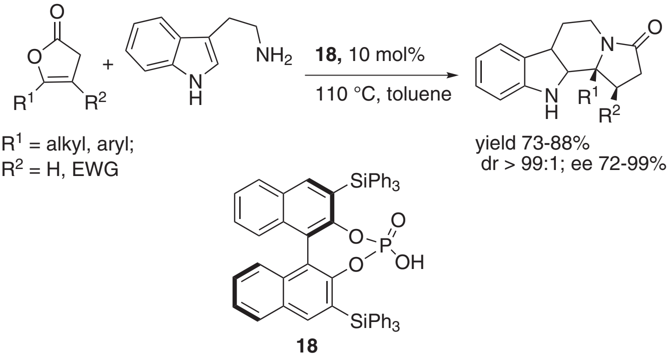
Scheme 26.8 Atroposelective organocatalytic reaction developed by Rueping.

The product exhibits a remarkable atropisomerism [61] determined by the rotation barrier around the bonds of quaternary carbon center. After optimization of the reaction conditions with different phosphorous triflamides and by varying the temperature, solvent, catalyst loading, and concentration, the bis indole **17** was obtained with a remarkable 72% ee. In the supposed mechanism, a stabilized vinylic carbenium indolyl intermediate (Figure 26.4) undergoes a S_N1-type reaction by formation of a diastereoisomeric ion pair.

Terada and Akiyama independently introduced chiral phosphoric acids [62]. These compounds have become some of the most versatile chiral Brønsted acid catalysts, and have been applied to a broad range of enantioselective transformations [63].

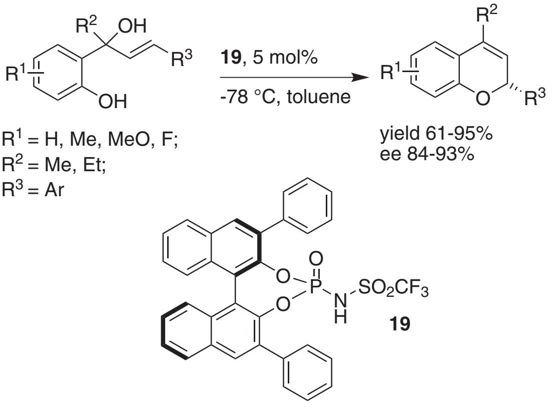
The discrimination of the face of the chiral carbenium ion is determined by the hindrance of the flanking groups. In the case of chiral Brønsted acids, the chiral counter ion, formed after effective protonation or partial donation of the proton, surrounds the created cationic intermediate. One face of the intermediate is effectively covered by the chiral counter ion and the nucleophile reacts with the less covered face. However, in many S_N1-type transformations mediated by Lewis acids, a transition state in which a couple of protons interact with the phosphates is often invoked. This double interaction seems crucial and only a partial success in the use of nucleophiles was achieved. Nevertheless, a series of successful S_N1-type reactions were discovered and are highlighted in this section. The chiral ion pairs between phosphate anions and iminiums [64] or metal ions were developed [65]. This powerful strategy is called asymmetric counteranion-directed catalysis (ACDC) and it has been applied successfully to several innovative transformations. The generation of carbenium ion *in situ* from alcohol, with the use of acids able to form a tight chiral ion pair with the phosphate anion, can be used in S_N1-type reactions. However, as previously discussed, only carbenium ions with good stability and moderate electrophilicity can be used. (1*H*-Indol-3-yl)(aryl)methanols can form a stable carbenium ion in the presence of a Brønsted acid, and Guo, Gong, and coworkers have used these carbenium ions, generated by chiral phosphoric acids, with enamides [66].

Enamides are suitable nucleophiles for this reaction because the Lewis basic phosphoryl oxygen can activate the enamide by a hydrogen-bonding interaction. High yields and excellent enantioselectivity were obtained in this reaction with different substituted indole rings. The electron-donating substituent on the 5-position of the indole gave better stereoselectivity, while the introduction of an electron-withdrawing group resulted in a slight decrease in enantioselectivity. The high degree of stabilization of the carbenium indolyl intermediate makes possible its nucleophilic interception. Ricci and Bernardi presented a Brønsted stereoselective Povarov reaction in which carbenium intermediates are generated from vinyl indole [67]. The idea was generally exploited by Terada, who envisioned the enantioselective addition of a nucleophile to the double bond of 3-vinylindoles, via the formation of stabilized carbenium ions [68]. The enantioselective addition reaction of azalactones to 3-vinylindoles catalyzed by a chiral Brønsted acid gave interesting products that can be readily converted into β-substituted tryptophan derivatives. The products were obtained in highly *syn* diastereo- and enantioselectivity with adjacent quaternary and tertiary stereogenic centers. Rueping presented a Brønsted acid catalyzed nucleophilic substitution of γ-hydroxy lactams with indoles [69]. The reaction was proposed to proceed via an intermediate *N*-acyliminium ion. The reaction needed the use of the more acidic *N*-triflylphosphoramide and good yields and up to 84% ee were obtained with the formation of quaternary substituted stereogenic centers. With similar results, Zhou used chiral phosphoric acids to promote the addition to indoles of 3-hydroxyisoindolin-1-ones [70]. The reaction of other different nucleophiles can be promoted by chiral phosphoric acids through intramolecular attack on an *N*-acyliminium ion, and a cascade reaction occurring between an *N*-acyliminium ion generated via a chiral Brønsted acid was described. (Scheme 26.9) [71].



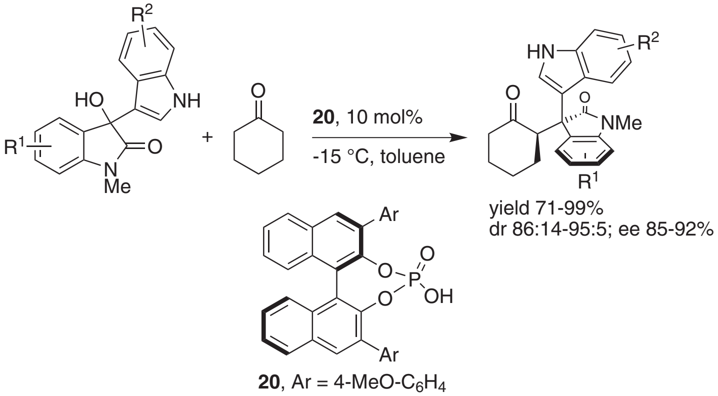
Scheme 26.9 Organocatalytic stereoselective acyliminium cascade.

Bach described the reaction of indoles and various methyl substituted indoles with another compound able to form a stabilized carbenium ion when it was treated with a chiral phosphoric acid. Secondary hydroxybenzylic alcohols derived from *p*-methoxy and dimethylamino 2-phenylaldehydes were prepared and treated with indole in the presence of chiral Brønsted acids [72]. An interesting reaction promoted by a chiral Brønsted acid was described by Antilla [73]. An indolyl diol was treated in the presence of a chiral phosphoric acid, affording the vinylogous iminium intermediate. The carbenium ion formed undergoes a pinacolic rearrangement, where the migrating group is a phenyl or a phenyl substituted groups, transforming the indolyl diols into chiral α-indolyl ketones with almost quantitative yield and up to 96% ee. Although, principally, results in Brønsted acids catalyzed S_N1-type reaction have been obtained with indol derivatives, quite interesting results with allyl species were reported by Rueping [74]. The procedure developed allows an enantioselective intramolecular allylic substitution, catalyzed by a chiral Brønsted acid (Scheme 26.10).



Scheme 26.10 Metal-free allylic substitution promoted by a chiral contact ion pair.

The substrates prepared, 2*H*-chromenes, were obtained in good yields and with excellent enantioselectivities. The reaction proceeds using *N*-triflylphosphoramide **19** as Brønsted acid and the process exhibits compatibility with the presence of a wide range of substituted aromatic rings. The carbenium allyl intermediate is associated with the phosphoramide anion in a chiral contact ion pair. Not only oxygen can be a nucleophile in organocatalytic Brønsted acid promoted S_N1-type reactions as Huang and coworkers [75] described intermolecular enantioselective *N*-alkylation of indoles with α,β,-unsaturated γ-lactams as electrophiles (up to 95% ee). Conceptually, the reaction is based on the formation of a cyclic *N*-acyliminium ion, with subsequent interaction of the N–H function of the indole with the conjugate base of the chiral Brønsted acid. The direct palladium-free catalytic α-allylic alkylation of aldehydes in the presence of achiral amine (Et_2NH 10 mol%) and *p*-TSA (20 mol%) was described by Xu and Lai [76]. Branched and unbranched aldehydes can be used in the reaction, which was performed in CH_3CN. However, despite the use of many chiral amines, no enantiomeric excess was recorded for the reaction. The use of only Brønsted acids instead of enamine catalysis for aldehyde activation was recently disclosed in achiral form [77]. The authors selected *p*-MeO-diaryl-methanol as a model substrate that is rarely considered in previous studies in this field. In fact, the corresponding carbenium ion is less stabilized and taken as a reference compound ($E = 0$) in the Mayr scale. Less stable carbenium ions were also used in the study when the reaction was promoted by triflic acid. Although the reaction was developed in achiral form, quite interesting points were established for further development. *p*-Toluenesulfonic acid (*p*-TSA) in CH_2Cl_2 is able to mediate the reaction, while weak acids, such as acetic acid, are ineffective. ^{t}BuOH (1 equiv.) is used as additive, to reduce the formation of ketones and alkane (self-redox reaction) often observed in S_N1-type reactions [78]. Notably, the reaction pathways were briefly explored by means of DFT calculations. Interestingly, the interconversion of the diphenyl methyl cation intermediate into the corresponding ether side product is facile, requiring relatively low activation energy. Ether by-products are often observed in many S_N1-type reactions, and the reversible ether formation itself does not affect the reaction course. Unfortunately, it was difficult for the authors to find an enantioselective transformation, which is probably owing to the inefficiency of phosphoric Brønsted acid to promote the process. However, very recently Guo and Peng [79] found a solution for this important problem, considering again 3-indolylmethanols as ideal substrates (Scheme 26.11). To observe the reaction they had to manage the electrophilicity of the carbenium ion. In fact, by introducing an electron-withdrawing group on 3-indolylmethanol that leads to an increase electrophilicity they observed the desired product.

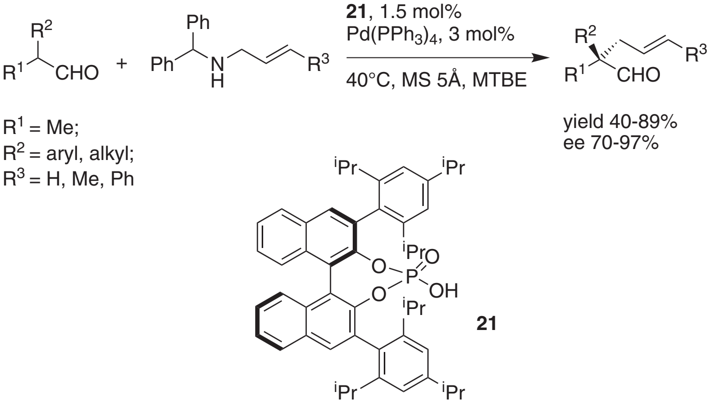


Scheme 26.11 Asymmetric alkylation of ketones promoted by chiral Brønsted acids.

They selected the isatin-derived 3-hydroxy-3-indolyoxindole as a good alkylation reagent for the direct alkylation reaction. Quite remarkably, the stereoselective reaction promoted by chiral phosphoric acid was described with ketones and not with aldehydes, owing to the major tendency of ketones to form the enol by acid catalysis. The reaction proceeded smoothly and the desired alkylation products were obtained in good yields with high diastereoselectivity and enantioselectivity. A phosphoric acid bearing electron-rich *para*-substituted phenyl groups on the 3,3′-position had better catalytic activity in this reaction. The substrate scope of various cyclic and acyclic ketones in this reaction was also investigated and remarkably the latter were also suitable for this alkylation reaction. An in-depth investigation of the substrate gave some indication of the possible intermediate. *N*-Benzyl-3-hydroxy-3-indolyloxyindoles were synthesized and used in the reaction, but the yield and enantioselectivity greatly decreased. For the author this result was an indication that the 3-hydroxy-3-indolyloxindole underwent this reaction via a vinylogous imino intermediate. The transition state suggested to explain the stereochemical outcome of the reaction underlies the important interaction established with the chiral phosphoric acid. In many stereoselective reactions the chiral acid can interact with both the electrophiles and the nucleophiles. In this reaction the chiral phosphoric acid is linked to the enol form of the ketones and to the proton of the vinylogous indolyl carbenium cation. Other substrates in organocatalytic S_N1-type reactions were considered as well. Rios has reported the alkylation of oxazolones through a S_N1-type reaction by using alcohols able to form stabilized carbenium ions. The reaction was catalyzed by Brønsted acids, such as TFA, to afford the final compounds in excellent yields [80].

26.6.1
Organocatalytic S_N1-Type Reactions with Brønsted Acids and Metals

List has developed the concept of asymmetric counter-ion directed catalysis and applied it in organocatalytic transformations. One of the first pioneering studies in the synergic use of organocatalyst and transition metal was the combination of a Pd(0) catalyst with a chiral phosphoric acid in a highly enantioselective Tsuji–Trost type α-allylation of branched aldehydes (Scheme 26.12) [81].



Scheme 26.12 Chiral counteranions in organocatalytic S_N1-type reactions.

Formation of the allylating reagent was induced by the condensation of a secondary allylamine with the branched aldehyde, in the presence of a catalytic amount of a chiral phosphoric acid. The enamonium phosphate form, in the presence of the palladium salt, is transformed into the corresponding allyl palladium complex bonded to the chiral phosphoric counter ion. Finally, enamine nucleophilic attack on the formed π-allyl palladium complex occurs in enantiospecific fashion. Recently, List has further enhanced the scope of the chemistry by developing the first highly enantioselective direct α-allylation of α-branched aldehydes with allylic alcohols. Effective asymmetric induction is realized through the incorporation of a chiral phosphoric acid within the activated complex, following an ACDC strategy. The reaction efficiently creates all-carbon quaternary stereogenic centers in a single step, from readily available precursors. In this study the major achievement was the possibility of using simple allylic alcohols without the need for an additional chemical step [82]. An approach to chiral 2,3-disubstituted indolines by asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles was realized by combining a reductive alkylation (Friedel–Crafts/dehydration/reduction) of 2-substituted indoles with aldehydes. The process can be realized in a stereoselective manner through consecutive reductive alkylation/hydrogenation reactions promoted by a Brønsted acid/Pd-phosphine complex, with up to 98% ee [83]. Experiments conducted with ESI-MS indicated that the reaction is reversible and a bisindole is formed in the reaction mixture. The vinylogous iminium carbenium ion previously discussed is clearly involved in this transformation. Terada has reported a relay catalysis for a carbonyl ylide formation/enantioselective reduction sequence using a binary catalytic system that consists of the dirhodium(II) tetracarboxylate and a chiral phosphoric acid as a Brønsted acid catalyst. The proposed relay catalysis involves a four-step transformation. Decomposition of the α-diazocarbonyl compound generates the rhodium carbene complex and subsequent intramolecular cyclization gave the carbonyl ylide equivalent. Reduction of the pyrylium cationic intermediate using the Hantzsch ester is under the influence of the chiral counter ion. The hydride can be considered as the nucleophile in this S_N1-type reaction, in which the stable pyrylium cation is formed [84].

26.7

S_N1-Type Reaction Promoted by Chiral Thioureas

Hydrogen bond donating (HBD) catalysis has emerged as a biomimetic alternative to Lewis acid activation. These reactions usually employ ureas or thioureas as key functional groups capable of two-point hydrogen bonding with acidic N–H bonds. Numerous bond-forming reactions (e.g., Friedel–Crafts reactions, Claisen rearrangements, Diels–Alder reactions, Strecker reactions, Mannich reactions, conjugate additions, and others) can be catalyzed by homogeneous HBD catalysts, often in excellent yields and selectivities [85]. New routes in organocatalysis were discovered by Jacobsen, who introduced chiral hydrogen-bond donors able to effectively promote the highly enantioselective reactions of cationic intermediates. The

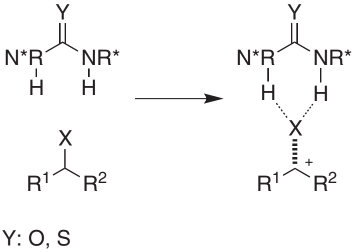
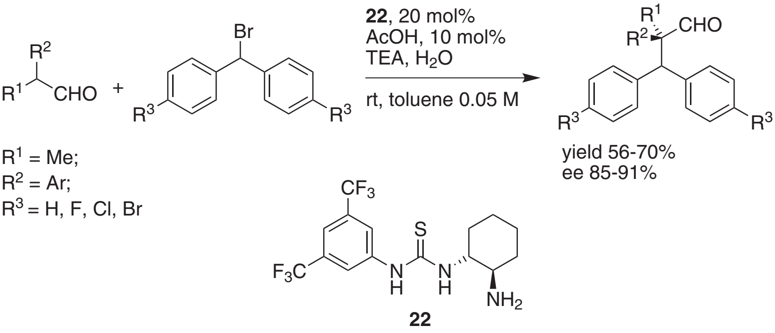


Figure 26.5 Formation of carbenium ion induced by hydrogen bonding.

ability of chiral thiourea to activate the substrates and to efficiently block a face of the generated cationic intermediate was used to promote various interesting transformations. This process is successful thanks to the ability of urea and thiourea catalysts to bind an anion associated with a charged electrophile, through hydrogen-bond interactions. The formation of the tight ion pairing ensures that the chiral catalyst remains in close proximity to the charged electrophile during the enantioselectivity-determining step of the catalytic cycle (Figure 26.5).

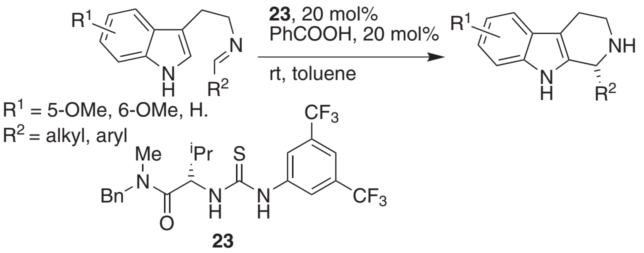
These secondary interactions are present even in enzymes such as oxidosqualene cyclase, which can stabilize the cationic intermediates by cation–π interactions. However, in the design of these catalysts a critical element needs to be present. In many of the catalysts designed by Jacobsen, the presence of aromatic group is useful to direct the stereochemical results, in particular an increase in the efficiency of the reaction was observed when large arenes were employed [86]. Most of the work described by Jacobsen was directed to the generation of heteroatom-stabilized carbocations, such as *N*-acyliminium and oxocarbenium ions; in addition, the alkylation of branched aldehydes with bromo diaryl derivatives was also described (Scheme 26.13) [87].



Scheme 26.13 Alkylation of aldehydes with benzhydrylic bromides.

The presence of a primary amino group in a catalyst was shown to be necessary for catalysis in the present case where the enamine of the branched aldehyde was involved. The thiourea also plays an essential role in promoting the reactivity by generating the electrophilic partners. In the reaction with branched aldehydes, thiourea is generating highly electrophilic carbenium ions. As a unique case of S_N1-type reactions promoted by organocatalysts, quite electrophilic carbenium ions can be used. Notably, less stabilized carbenium ions gave the desired product in racemic form, probably because more stable carbenium ions are less tightly connected to the thiourea and so no stereoinduction was observed.

The formation of *N*-acyliminium ions by a thiourea-mediated catalytic reaction was investigated with β-indolyl ethyl hydroxylactams. The generation of the *N*-acylimminium in the presence of an indole can be successfully used in a Pictet–Spengler-type cyclization of such compounds, affording highly enantioenriched indolizidinones and quinolizidinones (Scheme 26.14) [88].



Scheme 26.14 Enantioselective Pictet–Spengler-type cyclization.

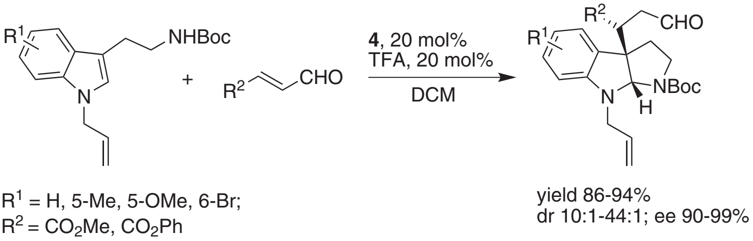
A set of model reactions were examined and, through analysis, an optimal catalyst was found. The acylimminium was generated by the use chlorotrimethylsilane or the combination of HCl and 3 Å molecular sieves. The addition of indole to hydroxylactam-derived cyclic N-acyliminium ions under the catalysis of a thiourea Schiff base derivative was reported by Jacobsen [89]. Various thiourea and urea catalysts were evaluated by a systematic variation of their structure. Introduction of an aryl group able to interact in polar–π interactions with the acylimminium ion improves the enantioselectivity of the reaction. The chlorine leaving group necessary to establish formation of the acylimminium was obtained by reaction with TMSCl. The presence of a catalytic amount of water improves yields and stereoselectivity, suggesting that HCl generated *in situ* is the chlorinating reagent. Based on a S_N1-type reaction Jacobsen described an asymmetric polycyclization promoted by thiourea catalysis [90]. The bicyclization of hydroxylactams was carefully developed in conjunction with thiourea catalysts that showed good cation–π interactions.

26.8

S_N1-Type Organocatalytic Reaction of Iminium, Oxonium, and Aziridinium Intermediates

The reactivity discovered by Jacobsen with chiral thiourea is fully consistent with S_N1-type chemistry. Besides the formation of reactive *N*-acyliminium species, related oxocarbenium species can be formed and reacted in a similar way. In fact Jacobsen reported application of the thiourea activation mode to the generation of oxocarbenium ions [91]. Before S_N1-type reactions became a hot topic in stereoselective organocatalysis, Jacobsen has already discovered and introduced the possibility of using the S_N1 pathway for highly enantioselective transformations. Although diastereoselective additions to substituted oxocarbenium ions were also reported [92], the reaction between 1-chloroisochromanes, obtained *in situ* by the reaction of the corresponding methoxo derivative with BCl_3, with silylenolates was described to obtain the desired products in excellent yield and high enantiomeric excesses. The stabilized carbenium species containing oxygen were generated with the use of thiourea by Jacobsen and employed in cycloaddition reactions. This was the case for the oxidopyrylium, generally accessed by thermolysis of the corresponding acetoxypyranone [93].

Anion metathesis, wherein a silver salt of a chiral anion can abstract a halide from an organic fragment to produce a chiral ion pair, was recently proposed by Toste in the generation of aziridinium and episulfonium ions. The resulting cationic intermediate could then be intercepted by a nucleophile in an enantioselective manner directed by the chiral counteranion. The cationic intermediates were opened by alcohols in a highly enantioselective manner [94]. Another type of uncommon electrophilic iminium was recently considered in the development of organocatalytic S_N1-type reactions. The generation of this quite reactive and versatile intermediate is connected with the chemistry of indols [95]. Generally, an indole reaction at the C3 position can be considered as an enamine-type of reactivity. The intermediate iminium, obtained after nucleophilic attack at the C3 position, can be susceptible to nucleophilic reaction due to temporary electrophilicity at the C2 position of the indole moiety. Indolines are generally obtained with the two subsequent reactions and the strategy has been employed in the synthesis of natural products. For example, this strategy was first adopted in the synthesis of tricyclic frameworks, such as pyrroloindolines, by MacMillan and coworkers (Scheme 26.15) [96].



Scheme 26.15 Organocatalytic construction of pyrroloindoline.

Another elegant example was demonstrated by the same authors in the enantioselective total synthesis of (+)-minfiensine, through an iminium activation that allows a Diels–Alder cyclization step to generate the tetracyclic structure with very high stereocontrol [97]. An organocascade reaction performed in the presence of a cinchona primary amine derivative was developed by You [98]. In the reaction, tetracyclic indolines in high enantiomeric excesses were obtained; this route was employed in the synthesis of a natural product analog. Spirocyclic compounds derived from oxindole can be accessed by the activation mode discussed. Barbas, in fact, reported the enantioselective synthesis of carbazole spirooxindole derivatives by catalysis with a thiourea, in which the possible pathway involves the indolenine intermediate generated from the vinylogous enamine [99].

26.9
Conclusions and Perspectives

Organocatalytic S_N1-type reactions in which chiral nucleophiles (enamines) or a chiral environment (by thioureas and chiral Brønsted acids) are formed are now well-established procedures in organocatalytic transformations. The facile generation of carbenium ions can be used advantageously to form quite reactive electrophiles under mild reaction conditions. However, a general solution for the very reactive carbenium ion needs to be found, to enhance the scope of this chemistry. Although the use of metals like calcium [100] and tin [101] seems to be quite promising, the compatibility of these metals in organocatalytic processes awaits further studies. In addition, new chiral and more accessible counter ion backbones need to be found. Certainly, the application of organocatalytic multicomponent reactions in which carbenium ions are formed *in situ* and reacted can constitute a further goal for these fields of research.

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27

Alpha-Heteroatom Functionalization of Carbonyl Compounds

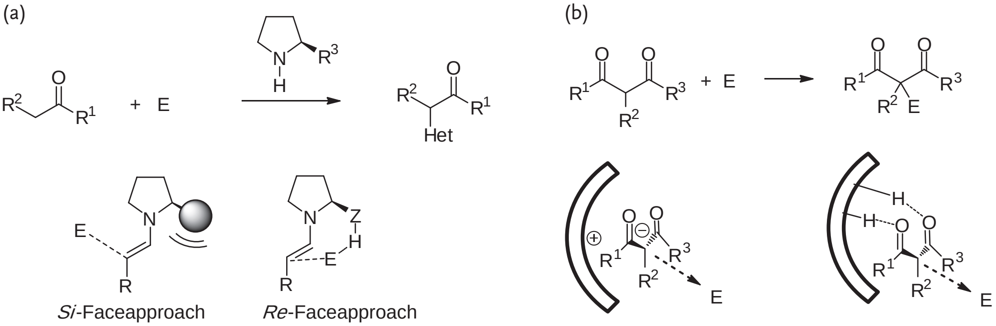
Gabriela Guillena

27.1

Introduction

The methodology known as direct α-heterofunctionalization of carbonyl compounds was comprehensively reviewed in 2006 [1] and therefore only the most recent developments [2] in this research area since then are considered in this section. These will be presented by the reaction that led to the formation of the new carbon–heteroatom bond, excluding of those in which the hybridization of the previously functionalized carbonyl compound is modified.

Several mechanisms, depending on the type of catalyst used, have been proposed to achieve the effective activation of the α-carbon of the carbonyl compound (Scheme 27.1). The use of a chiral primary or secondary amine as organocatalysts led to the formation of a nucleophilic enamine, which then reacts with the electrophilic heteroatom to give the new C–heteroatom bond. Two different types of interactions, steric or electronic, generated by the nature of the substitution at the chiral amine determine the stereochemical outcome of the reaction. Thus, for proline and their derivatives [3], the approach of the electrophile by the *Si*-face is forced by the steric shielding of the *Re*-face of the enamine by the substituent at



Scheme 27.1 (a) Modes of approach of the electrophilic heteroatom to the chiral enamine intermediate; (b) electrophilic heteroatom approach by non-covalent interactions to chiral catalysts.

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the 2-position. Meanwhile, the presence of an acidic proton on the substituent directs the approach of the electrophile by a hydrogen bond interaction between this acidic proton with the lone pair of the heteroatom, with the addition taking place by the *Re*-face of the enamine.

On the other hand, non-covalent interactions [4] have been proposed to justify the stereochemical control of the process when Brønsted bases or acids and phase-transfer catalysts [5] are used to promote these types of reactions, especially when 1,3-dicarbonyl compounds [6] were used as substrates. While the formation of chiral ion-pairs governs the heteroatom approach for basic catalysts, the formation of hydrogen bonds is responsible in the case of chiral Brønsted acids. In both cases, the effective shielding of one face of the nucleophile by the chiral catalyst determines the formation of the optically active product.

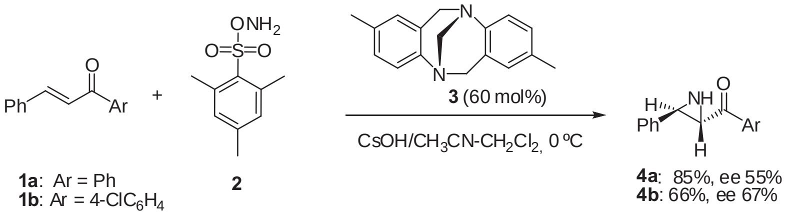
27.2
Enantioselective α-Pnictogenation of Carbonyl Compounds

27.2.1
Amination of Carbonyl Compounds

Nitrogen-atom containing molecules are well represented in Nature as a feedstock to build the constituents of life. In addition, most synthetic pharmaceutical products bear a nitrogen atom in their structures. Consequently, strategies to incorporate a nitrogen functional group into a molecule are of major interest in organic chemistry [7]. Organocatalytic methods offer two different ways to achieve this goal: via the aziridination of a α,β-unsaturated carbonyl compounds and further opening of the chiral aziridine [8], or via direct electrophilic amination at the α-position of a carbonyl compound [9].

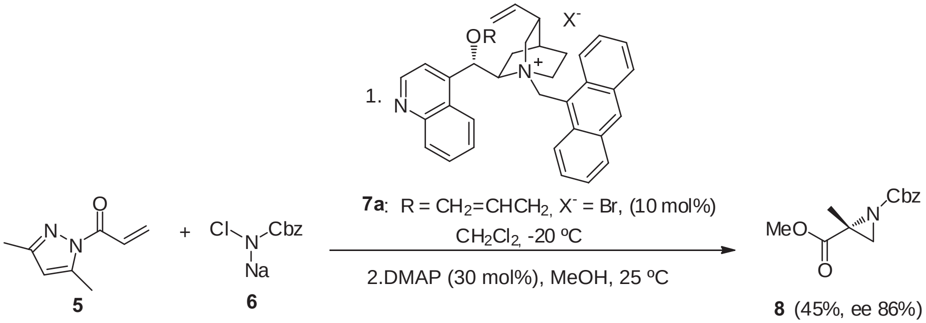
27.2.1.1 Aziridination of α,β-Unsaturated Carbonyl Compounds

The first reported organocatalyzed synthesis of chiral aziridines was carried out using cinchona alkaloids derivatives as phase-transfer catalysts [5], with moderate results. In addition, Tröger's base **3** was used as catalyst to form an aminimide derived from *O*-mesitylenesulfonylhydroxylamine (**2**) in a synthetic strategy to perform the aziridination of chalcones **1**, affording chiral aziridines **4** with moderate results (Scheme 27.2) [10]. Similar results (64% yield and 56% ee for **4a**) were obtained, using 105 mol% of quinine as catalyst [11].



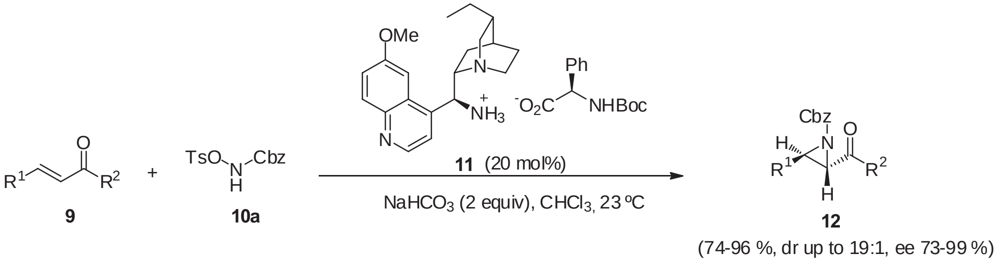
Scheme 27.2

Better levels of enantioselectivity have been achieved using different carbamates as nitrogen-atom source to perform this transformation. Hence, using *N*-chloro-*N*-sodium benzylcarbamate (**6**) and cinchoninium salt **7a**, as a phase-transfer catalyst, in the aziridination of dimethylpyrazole acrylate **5** afforded the corresponding aziridine [12], which was further treated with *N*,*N*-dimethylaminopyridine (DMAP) to give the methyl-ester substituted aziridine **8** (Scheme 27.3). The use of the pseudo-enantiomeric cinchonidinium salt led to the aziridine with the opposite absolute configuration, as expected.


1.
OR
X⁻
N+
N
5
+
Cl
N
Cbz
Na
6
7a: R = CH2=CHCH2, X⁻ = Br, (10 mol%)
CH2Cl2, -20 °C
2.DMAP (30 mol%), MeOH, 25 °C
MeO
O
N
Cbz
8 (45%, ee 86%)

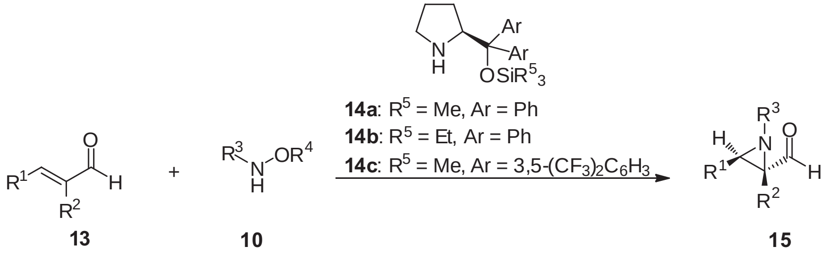
Scheme 27.3

Linear aliphatic and aromatic α,β-unsaturated ketones **9** were selectively aziridinated using salt **11** as catalyst and carbamate **10a** as nitrogen source (Scheme 27.4). These reaction conditions were also applied to several cyclic enones, leading to the corresponding aziridines with 85–99% ee, depending on the cycle size [13].


O
R1
R2
9
+
TsO
N
Cbz
H
10a
OMe
N
N
NH3+
⁻O2C
Ph
NHBoc
11 (20 mol%)
NaHCO3 (2 equiv), CHCl3, 23 °C
Cbz
N
O
H
R1
R2
H
12
(74-96 %, dr up to 19:1, ee 73-99 %)

Scheme 27.4

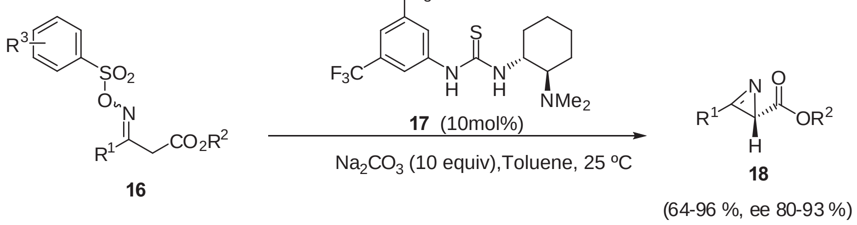
Prolinol-derived organocatalysts have been efficiently applied in the asymmetric aziridination of several types of α,β-unsaturated aldehydes (Scheme 27.5). Catalyst **14a** promoted the formation of linear 2-formylaziridines **15** from aromatic α,β-unsaturated aldehydes with good results (54–78% yield, dr up to 10 : 1, 84–99% ee). Using this catalyst, and choosing carefully the hydroxylamine derivative, the aziridination of α-monosubstituted enals and disubstituted α,β-unsaturated aldehydes was possible [14]. The absolute configuration of the 2-formylaziridines **15** was attributed to efficient shielding of the *Si* face of the chiral iminium intermediate by the aryl groups of the catalyst, leading to the stereoselective *Re*-facial nucleophilic conjugate attack at the β-carbon atom of the electrophile by **10.** The so-formed chiral enamine intermediate produced a 3-*exo-tet* nucleophilic attack on the now electrophilic nitrogen atom, releasing acetic acid.


Ar
Ar
N
H
OSiR$^5_3$
14a: R^5 = Me, Ar = Ph
14b: R^5 = Et, Ar = Ph
14c: R^5 = Me, Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
O
R^1
H
R^2
13
+
R^3
N
OR^4
H
10
R^3
N
O
H
R^1
H
R^2
15

Scheme 27.5

Compound **14b** catalyzed the aziridination of aliphatic and aromatic α,β-unsaturated aldehydes with similar results to catalyst **14a** [15]. Worse results were achieved by using catalyst **14c** in the synthesis of terminal *N*-tosylaziridines [16]. The further oxidation of products **15** allowed the synthesis of chiral β-amino esters derivatives [14–16], whereas their reduction permitted the synthesis of chiral protected amino alcohols [16].

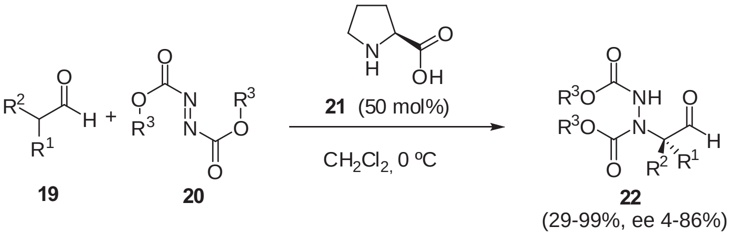
By means of organocatalytic methods, it is also possible to synthesize 2*H*-azirines, which are the smallest heterocycle containing a C=N in a three-membered ring, and which occur in some natural products. For this purpose, the Neber reaction of several β-ketoxime sulfonates **16** catalyzed by thiourea **17** was carried out, giving the corresponding 2*H*-azirines **18** with good results (Scheme 27.6) [17]. This reaction was applied as a key step in the synthesis of the antipode of natural dysidazirine, which was achieved in five steps with 75% yield and 93% ee.



Scheme 27.6

27.2.1.2 Direct α-Amination

The direct incorporation of a nitrogen-containing group at the α-position of a carbonyl compound is the most attractive way to accessing chiral α-amino acids, aldehydes, and alcohols. In this sense, organocatalytic direct α-amination has been well developed in the last decade and applied to a wide range of substrates, even to constructing molecules containing quaternary stereocenters [18] such as α,α-disubstituted amino acids, which are of great interest due to their biological activities. Thus, (*S*)-proline (**21**) was used as catalyst in the α-amination of α,α-disubstituted aldehydes **19** using azodicarboxylates **20** (Scheme 27.7) [19]. The best results, in terms of selectivity, were achieved using dibenzyl azodicarboxylate as a nitrogen source and α-alkyl α-aryl acetaldehydes bearing electron-donating groups. In contrast, non-aromatic α,α-dialkyl aldehydes gave compounds **22** in low enantiomeric excesses (4–39%). As compounds **22** were very labile, they could be further converted into the more stable corresponding (*R*)-oxazolidinones by an *in situ* reduction and cyclization. To reduce the high catalyst loading used and the long reaction times needed for completion, microwave conditions were applied to carry out this process [20]. When α-alkyl aryl aldehydes were used as substrates, irradiation with constant microwave power (200 W, 60 min, 60 °C) in acetonitrile as solvent enhanced the yields and enantioselectivities (54–97%, 52–90% ee) in shorter reaction times (from days to 60 min) compared to the process carried out at room temperature. Disappointingly, the catalyst loading (50 mol%) could not be reduced without compromising the yield and enantioselectivity. These reaction conditions were applied to several fluoro- or deutero-substituted aromatic and aliphatic aldehydes, achieving the corresponding fluorinated or deuterated α,α-disubstituted amino acid precursors in 63–97% yield and 53–90% ee [20b].



Scheme 27.7

The use of sulfonyl azides (RSO_2N_3) as electrophiles allowed the effective amination of α-branched aldehydes **19** by using (*S*)-proline (10 mol%) as catalyst and technical ethanol as solvent, affording the corresponding sulfamidated products (21–55% yield, 5–86% ee) [21]. The use of 2-nitrobenzenesulfonyl azide and α-alkyl α-aryl acetaldehydes gave the best enantiomeric excesses, whereas α-disubstituted alkyl aldehydes gave the highest chemical yields. The application of this procedure to linear aliphatic aldehydes provided the corresponding achiral sulfonyl imide. The absolute configuration of the products was determined, by X-ray diffraction, to be (*S*).

A mechanistic rationalization of the unusual product-acceleration behavior observed for the proline-catalyzed α-amination of linear aldehydes (**19a**, $R^2 = H$) was performed based on kinetic measurements [22]. Two parallel catalytic cycles were proposed: the conventional catalytic cycle and additionally a product-assisted cycle, where a highly reactive product–proline adduct is reversibly formed. However, from the kinetic data, the nature of this product–proline adduct could not be deduced. Therefore, computational calculations were required, suggesting a hydrogen bonded product–proline complex, resembling an "open" proline conformation, as responsible for the rate acceleration of the reaction.

Recently, DFT calculations showed that in this proline-catalyzed process an enamine carboxylic acid mediated transition model rules under base-free conditions, giving the expected product stereochemistry, while an enamine carboxylate pathway operates in the presence of base, leading to the opposite enantiomer [23].

The (*S*)-proline organocatalyzed α-amination of aldehydes using azodicarboxylates was applied as the key step in the synthesis of several interesting chiral compounds; for example, in the enantioselective synthesis of the tuberculostatic antibiotic (*S,S*)-ethambutol (**23**) [24], the effective drug for treatment of Parkinson's and Alzheimer's diseases (*R*)-selegiline (**24**) [25], some proteogenic and non-proteogenic amino acids such as (*R*)-pipecolic acid (**25**), (*R*)-proline (*ent*-**21**) [26], piperazic acid derivative **26** [27], the antibiotic (–)-anisomycin (**27**) [28], the synthetic alkaloid (–)-δ-coniceine (**28**) [29], and a precursor of the fungal natural product fumimycin **29** [30] (Figure 27.1). In addition, this transformation has been applied in the synthesis of a γ-secratase inhibitor metabolite (**30**) [31].

Other catalytic systems that differ from (*S*)-proline have been used in the α-amination of aldehydes using azodicarboxylates (Figure 27.2). Hence, (*S*)-4-*trans-tert*-butoxyproline (**31**, 5 mol%) was used as key step for the synthesis of several tetrahydropyridazines, which have been found in several bioactive peptides systems, in 70% ee [32]. Different aminal derived catalysts **32** (1 mol%) were used at room temperature in the α-amination of alkyl aldehydes, providing the expected products in 68–83% yield and 81–93% ee [33], showing a synergistic effect between the pyrrolidine and the aminal moieties. Ion-tagged proline derivative **33** (10 mol%)

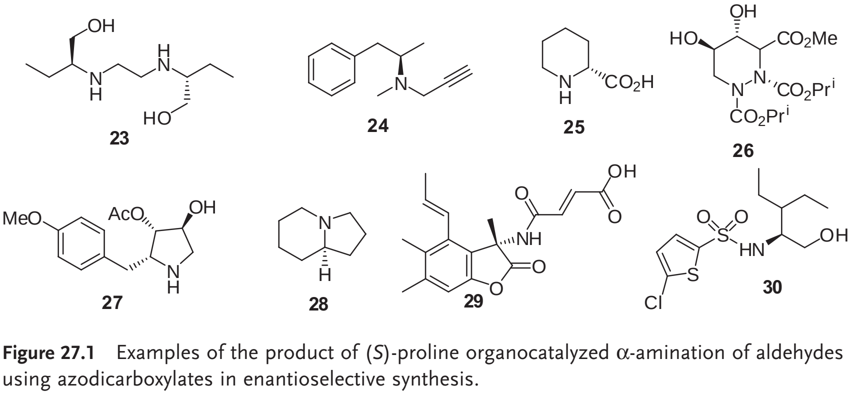


Figure 27.1 Examples of the product of (*S*)-proline organocatalyzed α-amination of aldehydes using azodicarboxylates in enantioselective synthesis.

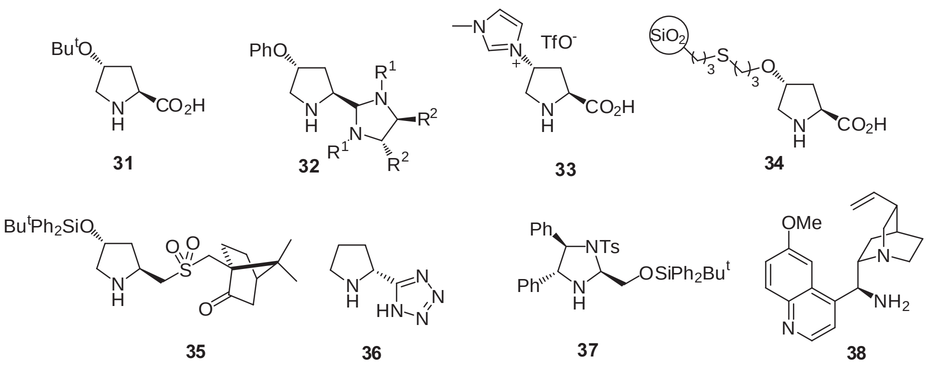
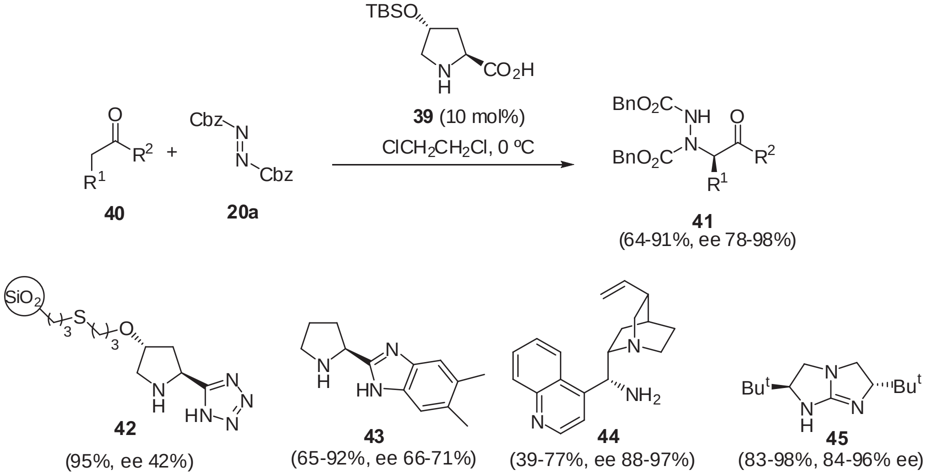


Figure 27.2 Catalytic systems other than (*S*)-proline employed in the α-amination of aldehydes using azodicarboxylates.

was used as catalyst for this transformation in [bmim][BF_4] (1-*n*-butyl-3-methylimidazolium tetrafluoroborate) as reaction media to give the aminated products in yields and enantioselectivities above 90%; the catalyst and solvent were reused up to four times without a detrimental effect on the results [34]. Worse results were achieved with the covalently supported (*S*)-4-*trans*-hydroxyproline derivative **34** under continuous flow conditions, providing the α-aminated isovaleraldehyde in only 58% ee, but in a high productivity, demonstrating the feasibility of using a flow regimen to achieve chiral products [35]. Excellent results were achieved using pyrrolidinyl-camphor derived catalyst **35** (5 mol%) in the α-amination of alkyl aldehydes, with worse results being encountered in the reaction of 2-phenylpropanal (**19**, R^1 = Me and R^2 = Ph; 46% yield, 75% ee) [36]. Tetrazole derivative **36** (50 mol%) was used in the synthesis of a key step intermediate of a stimulus-responsive amino acid, affording the expected products in 85% yield and 99% ee [37]. An aminal derived from chiral 1,2-diphenylenediamine (**37**) was tested as catalyst (10 mol%) in the α-amination of alkyl aldehydes using azodicarboxylates as nitrogen source, with the addition of one equivalent of acetic acid being compulsory to achieve the corresponding products in short reaction times [38]. Quinine derivative **38** (5 mol%) was applied in the α-amination of α,α-disubstituted aldehydes **19** using azodicarboxylates **20** (see Scheme 27.7), leading to products **22** in good results (72–96% yield, 36–99% ee) [39].

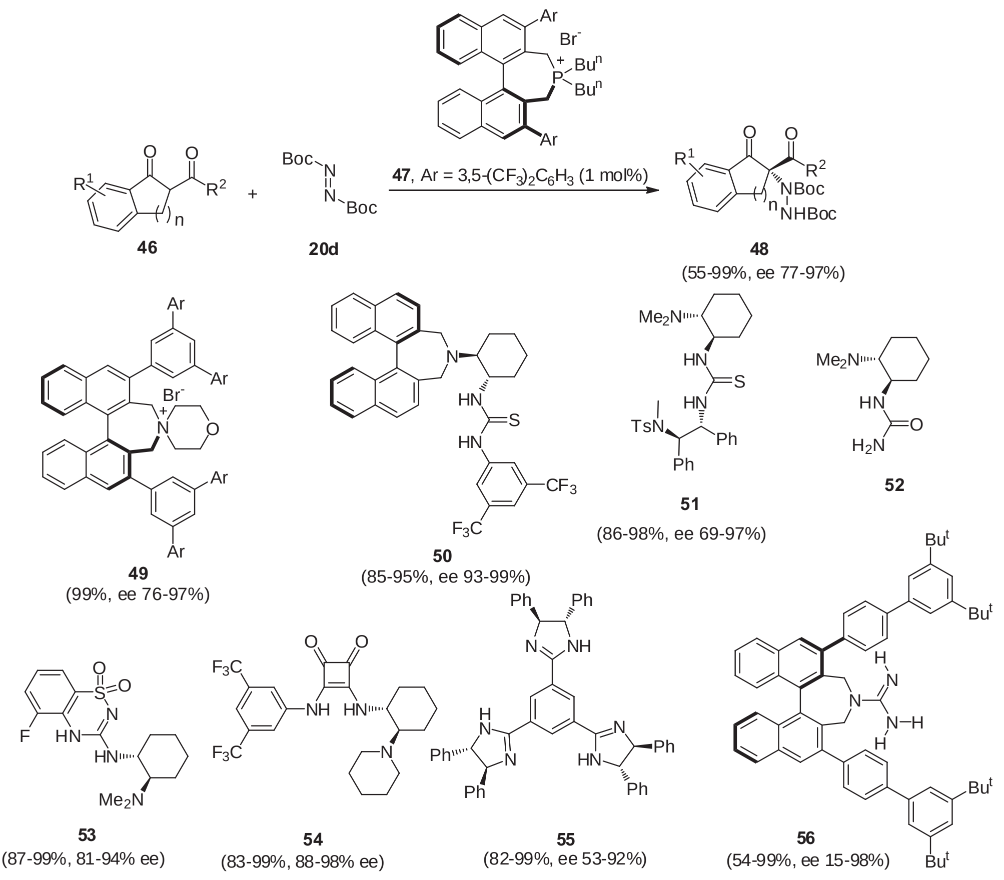
Complex molecules have also been synthesized by sequential use of the organocatalytic α-amination of aldehydes by azodicarboxylates catalyzed by some of the systems shown above and by other reaction processes, such as the Passerini reaction [40], Horner–Wadsworth–Emmons olefination [41], Wittig olefination [42], and allylation reaction followed by a ring-closing metathesis [43]. In addition, the combination of catalysts in cycle-specific organocascade processes [44] has allowed the synthesis of chiral complex molecules with good results.

The organocatalyzed α-amination reaction using azodicarboxylates can be also performed using ketones as substrates. Thus, silyloxyproline **39** promoted the reaction of several cyclic and acyclic ketones with dibenzyl azodicarboxylate (Scheme 27.8), with the addition of a small amount of water being need to achieve good results [45]. In contrast with the results achieved with aldehydes as substrates, a linear correlation between the enantiomeric excesses of the product versus the catalyst was found. To explain the enantioselectivity of the process quantum mechanical calculations were performed, suggesting that the most stable transition state was formed by the *anti* enamine reacting with the azodicarboxylate in the *trans* conformation. Other catalysts were tested in this type of transformation. Hence, a proline tetrazole derivative covalently bonded to silica gel (**42**) (10 mol%) promoted the amination of cyclohexanone with diethyl azodicarboxylate (**20b**) in acetonitrile as solvent [46]. Benzimidazole-pyrrolidine **43** combined with trifluoroacetic acetic (10–20 mol%) afforded the aminated products **41** in better results in dichloromethane at room temperature [47]. Cinchona alkaloid derived amine **44** (20 mol%), in combination with *p*-toluenesulfonic acid (40 mol%) and 4 Å molecular sieves, permitted the amination process using diethyl azodicarboxylate of aryl ketones in isopropanol as solvent, yielding at 40 °C the expected products with good results [48]. Bicyclic chiral guanidine **45** (10 mol%) catalyzed the amination of α-fluorinated aromatic cyclic ketones using 3-diethylpentan-3-yl azodicarboxylate (**20c**), providing the corresponding chiral quaternary fluorinated hydrazines with excellent results [49].



Scheme 27.8

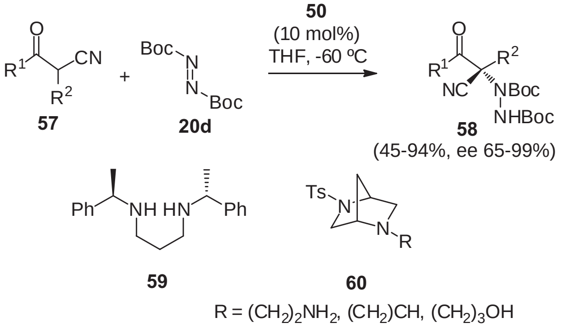
In addition, chiral nitrogen-substituted quaternary stereocenters can be accomplished by using 1,3-dicarbonylic compounds as substrates in the direct α-amination process. Thus, several cyclic β-ketoesters **46** (Scheme 27.9) were submitted to electrophilic amination under phase-transfer conditions catalyzed by the chiral binaphthyl phosphonium salt **47** [50a]. Different substituents on the aromatic ring were tolerated, but lower yields were obtained using a six-membered ring cyclic β-diketone. Under similar phase-transfer reaction conditions, compounds **48** were obtained with better results [50b,c] when catalyzed by chiral spiro-ammonium salt **49** [Ar = 3,5-$(CF_3)_2C_6H_3$].



Scheme 27.9

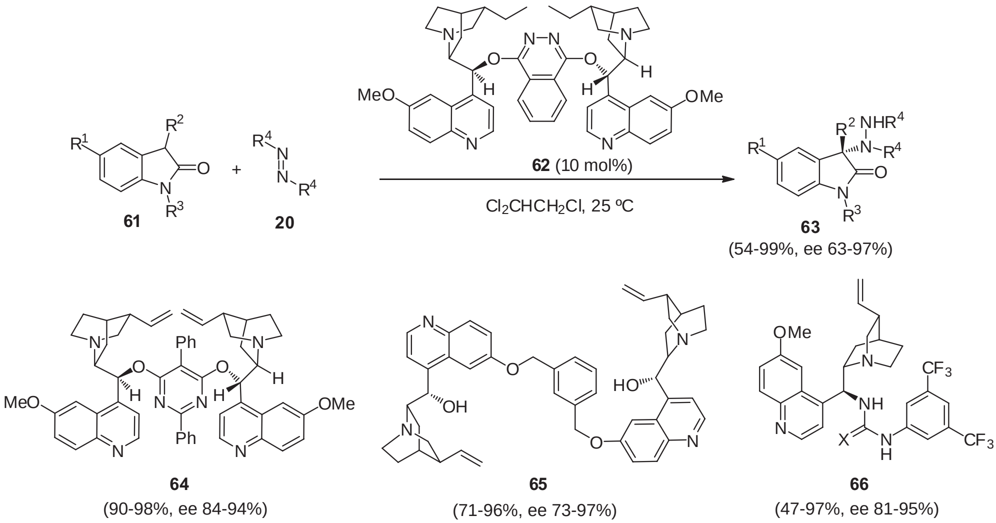
Good results were also achieved when bifunctional thiourea **50** (10 mol%) was used in the amination of cyclic *tert*-butyl β-ketoesters **46**, in toluene at −30 °C [51]. The use of amine-thiourea **51** (10 mol%), containing multiple hydrogen bond donors, in the amination of cyclic β-ketoesters [52] led to products **48** with good results. DFT studies performed for the reaction between 2-acetylcyclopentanone and dimethyl azodicarboxylate (**20e**), catalyzed with the bifunctional urea **52** [53], showed a mechanism that involved an initial nucleophile activation via protonation of the amino group and electrophile activation through substrate binding to the urea moiety and a subsequent C–N bond formation between these two activated components. This catalytic cycle ended with proton transfer from the protonated amino group to the adduct, followed by its dissociation to give the final product. The enantioselectivity of the reaction was controlled by the C–N bond-forming step, which was the rate-determining step. More effective than the urea in the reaction between azodicarboxylate **20d** and several cyclic β-ketoesters **46** was the quinazoline **53.** When catalyst **53** (10 mol%) was used in toluene, products **48** were obtained in high yields and enantioselectivities [54]. The use of squaramide derivative **54** allowed the catalysts loadings to be lowered to 2 mol%, giving excellent results [55]. The C_3-symmetry compound **55** (5 mol%) for the same reaction afforded the expected products in slightly worse results [56]. The electrophilic amination of several acyclic and cyclic β-ketoesters with di-*tert*-butyl azodicarboxylate (**20f**), using the novel chiral axially guanidine **56** (2 mol%), gave excellent enantioselectivities for five- and six-membered ring cyclic β-ketoesters **46** and good results with α-methyl acyclic β-ketoesters [57].

Catalyst **50** (10 mol%) has also been applied successfully in the electrophilic amination of cyclic and acyclic aromatic and aliphatic α-cyanoketones **57** [58], leading to the aminated products in good yields and excellent enantioselectivities (Scheme 27.10). Other chiral amines derived from α-phenylethyl amine, such as catalyst **59** (50 mol%) and diazabicyclo derivatives **60** (25 mol%), have been tested in the reaction of azodicarboxylate **20d** with phenyl α-cyanoacetate **57** (R^1 = Ph, $R^2 = CO_2R$) in toluene at −78 °C, affording the aminated products in similar results, up to 84% and 40% ee's (Scheme 27.10) [59]. The use of compound **56** (1 mol%) as catalyst promoted the amination of α-cyanothioacetates (**57**, R^1 = SEt) in good enantioselectivities (65–98%, 41–98% ee) [60].



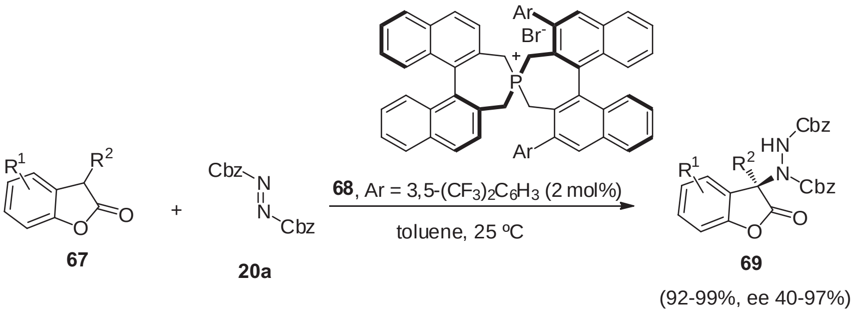
Scheme 27.10

3-Amino-2-oxindole compounds are core structures of some biological compounds with interesting pharmaceutical properties. They can be synthesized using the α-amination reaction of compounds **61** catalyzed by several cinchona alkaloids derivatives (Scheme 27.11) [61]. With the exception of dimeric catalyst **65** (5 mol%), which gave the best results in toluene as solvent and using the Boc-protected 2-oxindole (**61**, $R^3 = CO_2Bu^t$), the rest of the catalysts were used in halogenated solvents to afford unprotected products **63** in similar levels of yields and enantioselectivities. Whereas thiourea **66a** (X = S) showed a good performance in this type of transformation, the use of the related guanidine compound **66b** (X = NH, 10 mol%) allowed the amination of α-fluorinated β-ketoesters in excellent results (78–96%, 47–92% ee) [62].



Scheme 27.11

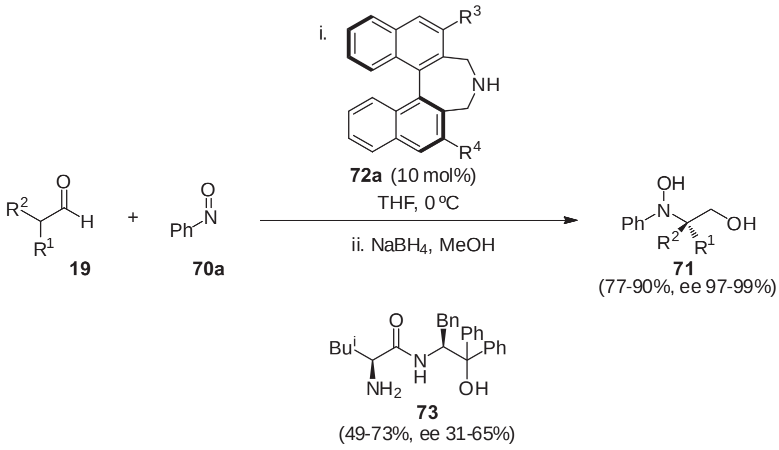
Benzofuran-2(3*H*)-ones are important building blocks for a vast number of natural products and drugs. The C3 position of this type of compound was functionalized by the electrophilic amination using a phosphonium-derived chiral salt (**68**), affording the expected products **69** in high yields and enantioselectivities (Scheme 27.12) [63].



Scheme 27.12

Another way to carry out the electrophilic amination of a carbonyl compound is by the reaction of an enamine or enolate with a nitroso derivative, the so-called hydroxyamination, oxyamination, or *N*-nitroso aldol reaction. The regio- and enantioselectivity of the transformation have been studied by DFT calculations for the reaction between achiral enamines and nitrosobenzene (**70a**) promoted by a chiral Brønsted acid catalyst, such TADDOL [64]. The results suggested a transition state that involves the enamine, nitrosobenzene, and two or more organic acid molecules, forming a cluster-like structure, where hydrogen-bonds play an important role.

Therefore, catalysts with low acidic protons, which are not able to protonate the nitrogen of the nitroso derivative, would promote the C–N bond formation by coordination of the oxygen atom of the N=O group, while more acidic catalysts promote the C–O bond formation. Thus, axially chiral secondary amine catalyst **72a** (10 mol%, $R^3 = R^4 = CHPh_2OH$) performed the hydroxyamination of linear aldehydes **19a** (R^2 = H) with nitrosobenzene (**70a**, Scheme 27.13) [65], with the resulting hydroxyamination product being reduced *in situ* to the corresponding alcohol using $NaBH_4$.



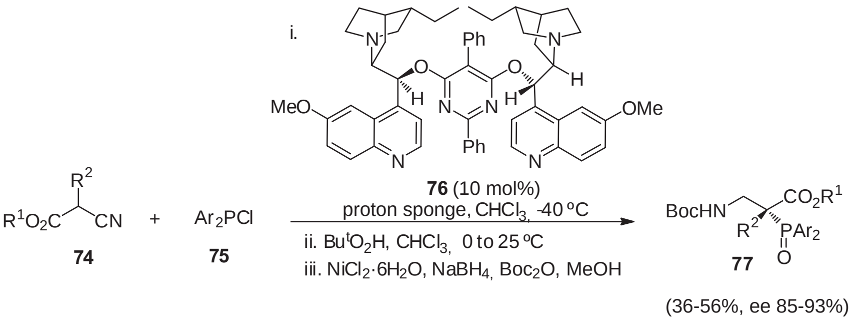
Scheme 27.13

Catalyst **14a** (20 mol%) led to products **71** (R^2 = H) in moderate yields and high enantiomeric excesses (40–75%, ee 91–99%) in the reaction of nitrosobenzene (**70a**) with linear aldehydes in dichloromethane at 0 °C [66a]. For this reaction, DFT calculations showed that the free activation energy $\Delta G^{\neq}$ for the non-catalyzed hydroxyamination was higher than that obtained in the presence of water or *N,N*-dimethylhydroxyamine, which mimics product **71** or its precursor. In addition, the $\Delta G^{\neq}$ values found for the catalyzed aminoxylation process are higher than those of the hydroxyamination. In this case, the observed (*S*)-preference for product **71** was rationalized by proposing an enamine intermediate with steric control approach from the *Si* face. Further calculations on the mechanism proposed that the lowest energy barrier proceeds via a *trans*-enol intermediate [66b], formed by two simultaneous hydrogen-exchanges between the aldehyde and the catalyst. This *trans*-enol formed, via hydrogen bonding, a complex with the catalyst, which is attacked by the nitrosobenzene from the *Si* face of the enol via a new transition state, determining the stereochemical outcome of the reaction.

Linear aldehydes (**19a**, R^2 = H) or α-branched aldehydes **19** can be selectively aminated by nitrosobenzene (**70a**) using chiral amino alcohol **73** (20 mol%) in dichloromethane at −20 °C, although with moderate results (Scheme 27.13) [67]. Catalyst **36** (20 mol%) was used in the amination of α-branched aldehydes **19** with nitrosobenzene (**70a**), but the regioselectivity towards product **71** was very low, with the exception of α-methyl-α-aryl substituted aldehydes [68]. α-Aryl-α-cyanoacetates **57** (R^1 = OBu^t, R^2 = Ar) were aminated with moderate enantioselectivities (63–90% yield, 5–59% ee) using cinchona alkaloids as catalysts [69]. Similar results were achieved for 2-oxoindoles **61** as substrates in performing the amination reaction using nitrosobenzene (**70a**), with better results being obtained by using thioureas of type **17** (51–91%, 75–90% ee) [70].

27.2.2
Phosphination of Carbonyl Compounds

Although organophosphorus compounds are widely used in several fields of chemistry, their chiral synthesis [71] through electrophile phosphination has only been recently described [72]. The reaction of α-alkyl-α-cyanoacetates **74** (R^1 = OBu^n) with diaryl phosphine chloride **75** can be performed by using catalyst **76** in the presence of an excess of 1,8-bis(dimethylamino)naphthalene as a proton sponge, affording compounds **77** after oxidative protection of the phosphine group, nitrile reduction, and nitrogen-Boc protection (Scheme 27.14). The only limitation of the reaction seemed to be the impossibility of using electron-withdrawing groups at the aryl phosphine substituent as they led to degradation in the oxidative step. The mechanism was suggested to occur through a nucleophilic attack of the quinuclidine moiety to the phosphine, leading to an intermediate that contains a highly electrophilic phosphorus. A subsequent base-induced nucleophilic displacement of the catalyst formed the C–P bond, with the HCl released absorbed by the proton sponge.


i.
Ph
MeO
OMe
N
O
H
Ph
R^2
R^{1}O$_2$C
CN
+
Ar$_2$PCl
74
75
76 (10 mol%)
proton sponge, CHCl$_3$, -40 °C
ii. Bu^{t}O$_2$H, CHCl$_3$, 0 to 25 °C
iii. NiCl$_2$·6H$_2$O, NaBH$_4$, Boc$_2$O, MeOH
BocHN
CO$_2$R^1
PAr$_2$
77
(36-56%, ee 85-93%)

Scheme 27.14

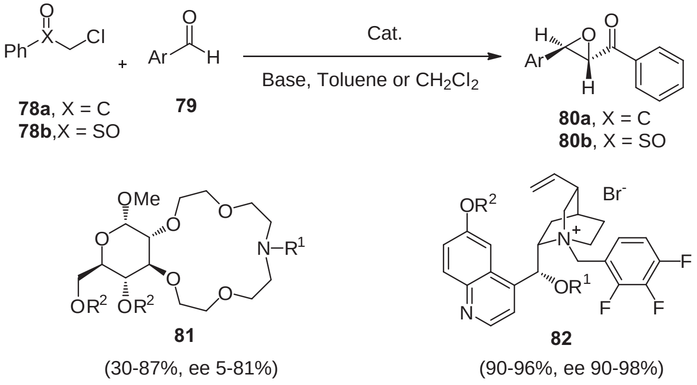
27.3
Enantioselective α-Chalcogenation

27.3.1
C–O Formation

Several natural products, as well as many versatile synthetic intermediates, have a carbon–oxygen bond at the α-position of the carbonyl compound. Therefore, synthetic strategies aiming to perform the stereoselective introduction of this carbon–oxygen bond are of great importance, and several organocatalytic methods have been developed recently.

27.3.1.1 Darzens Reaction

The Darzens reaction, involving a sequential aldol reaction followed by an intramolecular cyclization with control of the two newly formed stereogenic centers, is one of the most useful methodologies for the construction of chiral α,β-epoxy carbonyl compounds, which are useful synthetic intermediates. Phase-transfer catalysis performed by chiral ammonium salts has shown its efficiency in this transformation. DFT calculations for this reactions showed that the complex interaction energy is not a crucial parameter for the catalyst's selectivity as the complex stabilization energies and the achieved enantiomeric excesses did not correlate [73]. As an alternative to chiral ammonium salts, as phase-transfer catalysts, several aza-crown ethers derived from glucose (**81**) and mannose (10 mol%) have been applied as catalysts in the reaction between α-chloroacetophenone (**78a**) and aromatic aldehydes **79** in a toluene–aqueous alkaline two-phase system to give the corresponding chiral *trans* epoxy-ketone **80a** in moderate yield and enantioselectivity (Scheme 27.15) [74]. Instead of compound **78a**, other heteroaromatic α-chloroacetyl derivatives such as 2-chloroacetylfuran or 2-chloroacetylthiophene were also used in this reaction, with the best results achieved with the latter. The

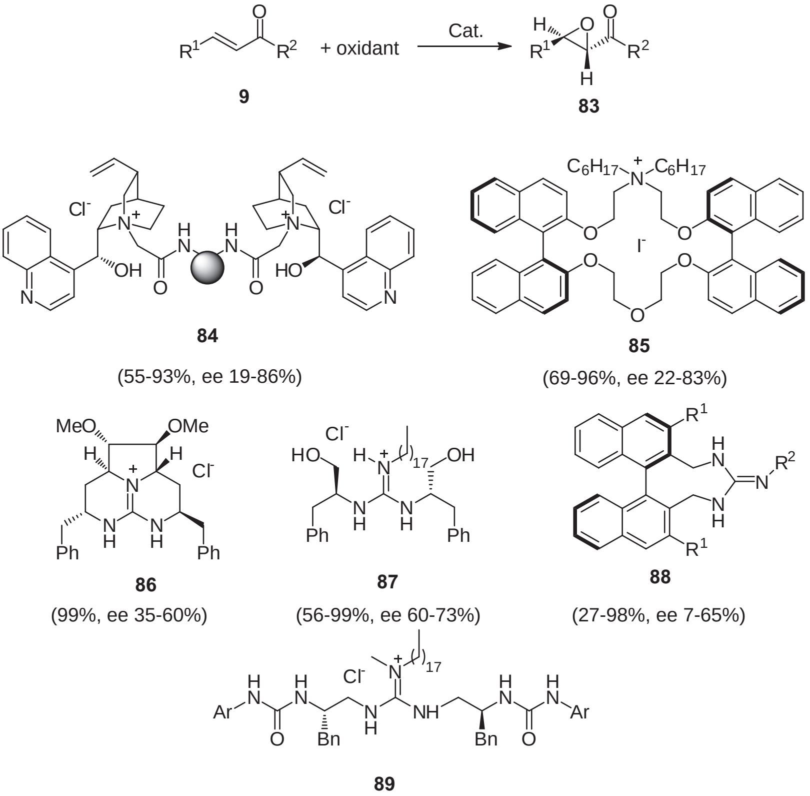


Scheme 27.15

use of ammonium catalyst **82a** (R^1 = 9-anthracenyl, R^2 = H, 10 mol%) in a dichloromethane–aqueous alkaline two-phase system allowed the synthesis of di- and trisubstituted epoxides of type **80** by the reaction of aromatic and even aliphatic aldehydes with several α-chloro ketones with excellent results [75]. The salt **82b** (R^1 = H, R^2 = Me, 10 mol%) has been used for the asymmetric synthesis of α,β-epoxy sulfonyl compounds **80b** in good yields and high enantioselectivities (80–95% yield, 71–97% ee) [76].

27.3.1.2 Epoxidation of α,β-Unsaturated Carbonyl Compounds

The asymmetric epoxidation of electron-poor alkenes, such as enones, has been developed significantly in the recent past [77] due to their importance as building blocks. Excellent levels of enantioselectivities have been obtained using polyamino acid derivatives (Juliá–Colonna catalyst) with molecular weights close to those of enzymes [78], and therefore beyond the scope of this chapter. In addition, chiral transfer reagents, especially those derived from cinchona alkaloids have been applied to this transformation in high efficiency and under mild reaction conditions using apolar solvents as a reaction media and NaOCl as oxidant [79]. Dimeric cinchona catalysts of type **64** (1 mol%) catalyzed the epoxidation of (*E*)-diarylenones **9** with hydrogen peroxide as oxidant, in high levels of enantioselectivities [80]; the length of the spacer between the two cinchona units and the use of different surfactants is crucial to achieving good results. Only moderate enantioselectivities were obtained in the epoxidation of (*E*)-diarylenones **9** with soluble chiral polymeric ammonium salts such as **84** (5 mol%, Scheme 27.16) anchored to diacetamido-PEG_{2000} chloride resins [81]. The aza-crown ether-type ammonium salt **85** [82] derived from (*S*)-BINOL was used as a successful catalyst for the epoxidation of (*E*)-electron-poor chalcones, whereas electron-rich chalcones were not suitable substrates. Guanidine base type structures are other phase-transfer catalysts that have been used in the epoxidation of (*E*)-enones **9.** Thus, tricyclic guanidine **86** (10 mol%) gave products **83** in quantitative yields and enantioselectivities, using *tert*-butyl hydroperoxide as oxidant in a liquid–liquid dichloromethane and aqueous potassium hydroxide two-phase system at 0 °C (22–99%, 35–60% ee) [83]. Acyclic hydroxy-guanidine **87** (10 mol%) led to higher enantioselectivities, with the observed stereoselectivity being explained by a transition state involving a hydrogen bonding coordination of the carbonyl group with the guanidine and an interaction of the hydroxy group with the *tert*-butyl hydroperoxide anion [84]. Several axial stereogenic guanidines **88** (10 mol%) were used in the enantioselective epoxidation of chalcone **1a** in the presence of 30% aqueous hydrogen peroxide in toluene at room temperature [85], with the best results being obtained by the incorporation of a chiral substituent on the nitrogen atom of the guanidine moiety. This compound (5 mol%) was used as catalyst for the α-amination of 1,2-oxoesters [86] to give the corresponding products with good results (36–90%, 93–94% ee) [87]. Under similar reaction conditions to those described with catalyst **88,** the guanidine-urea bifunctional catalyst **89** (5 mol%) was used for the epoxidation of (*E*)-enones **9**, affording the corresponding epoxides **83** in excellent results [88]. Furthermore, the catalyst can be recovered from the reaction mixture by



9

83

84
(55-93%, ee 19-86%)

85
(69-96%, ee 22-83%)

86
(99%, ee 35-60%)

87
(56-99%, ee 60-73%)

88
(27-98%, ee 7-65%)

89
(91-99%, ee 85-96%)

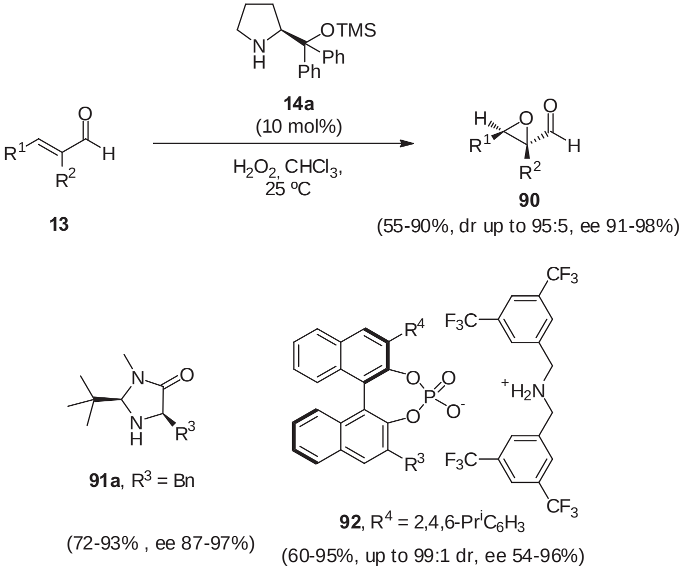
Scheme 27.16

chromatographic purification and was reused up to five times, giving the same level of enantioselectivity each time.

The epoxidation of (*Z*)-enones has been less developed using organocatalytic methods. However, simple cyclic enones, such as cyclohexenone, are suitable substrates for this reaction using hydrogen peroxide as oxidant and catalyst **38** (10 mol%) in the presence of trifluoroacetic acid (1 or 2 equiv) in dioxane at 30–50 °C [89], providing excellent results (33–85%, 78–99% ee). DFT calculations carried out for this transformation showed that the reaction proceeded via a sequential nucleophilic addition and ring closure processes involving a ketominium intermediate [90]. Similar reaction conditions were applied to perform the construction of key intermediates in the synthesis natural spirocyclic compounds [91]. The epoxidation of (*Z*)-cyclic enones was also performed by cinchona alkaloid derivatives under phase-transfer catalysis. For instance, 2-methylnaphthoquinone (vitamin K_3) was epoxidized in 85% enantiomeric excess [92].

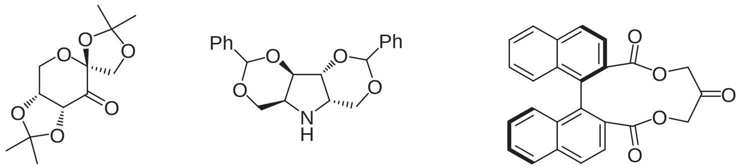
The epoxidation reaction of α,β-unsaturated aldehydes has only been successfully accomplished using secondary amine catalysts, with diarylprolinols, such as

14, being privileged structures to perform this task [93]. Thus, using catalyst **14a** (10 mol%, Scheme 27.17) and 50% aqueous hydrogen peroxide, several α,β-unsaturated aldehydes (**13**) were epoxidized in good yields and with high diastereo- and enantioselectivities in dichloromethane at room temperature [94]. In addition, β,β-dialkyl α,β-unsaturated aldehydes were suitable substrates for this reaction, affording the corresponding epoxides in good yields and diastereoselectivities, but with low enantioselectivities. Although these reaction conditions failed in the epoxidation of α,β-unsaturated ketones, other related diaryl-2-pyrrolidinemethanols promoted this transformation with high efficiency [95]. Indeed, even other more challenging substrates, such as 2-arylidene-1,3-diketones [96], 2-acyl-3-arylacrylonitriles [97], and α,β-unsaturated oxindole esters [98], were successfully epoxidized using different catalysts of type **14.** The use of these epoxidation conditions has permitted the development of several tandem transformations [94a, 99], which are especially useful for the synthesis of chiral heteroaromatic compounds [100].



Scheme 27.17

The epoxidation of α,β-unsaturated aldehydes has also been promoted by imidazolidinone **91a** (20 mol%) in combination with perchloric acid and (nosylimino) iodo benzene (NsNIPh) as hypervalent iodine oxidant in high yields and enantioselectivities [101], with only enals possessing an electron-withdrawing group being unreactive under these reaction conditions (Scheme 27.17). In addition, the new catalytic salt **92** (10 mol%), in combination with *tert*-butyl hydroperoxide, was used to catalyze the epoxidation of several α,β-unsaturated aldehydes, including β,β-disubstituted-α,β-unsaturated aldehydes, with good results [102].



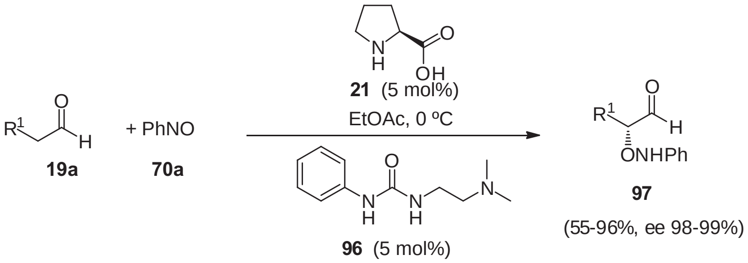
93 **94** **95**

Figure 27.3 Compounds used to promote the epoxidation of α,β-unsaturated aldehydes in the synthesis of chiral drugs.

The versatility of this reaction has been shown by its application as a key step for the synthesis of chiral drugs with interesting medical applications. Hence, fructose-derived ketone **93** (Figure 27.3) promotes the epoxidation reaction needed in the synthesis of an intermediate for the preparation of dipeptide isosteres with HIV inhibition and blood pressure modulation properties [103a] and for the antibiotic fosfomycin. This compound was obtained with better results using D-mannitol chiral amine **94** (100%, 74% ee) [103b]. The large-scale preparation of the key intermediate in the synthesis of anti-hypertensive agent diltiazem was accomplished by using chiral dioxirane **95** as catalyst [103c], showing the great potential of this methodology for industrial purposes.

27.3.1.3 Aminoxylation of Carbonyl Compounds

The direct organocatalytic α-aminoxylation reaction using nitroso compounds is one of the most attractive ways for the synthesis of chiral α-hydroxy carbonyl compounds. Control of the nitrogen versus oxygen electrophilic behavior, through the appropriate choice of catalysts and reaction conditions, is essential, with (*S*)-proline (**21**) being the epitome. Using aldehydes as substrates, in the reaction catalyzed by proline, the addition of bifunctional urea **96** to the reaction mixture increased considerably the reaction rate (Scheme 27.18) [104], probably due to a hydrogen bond interaction between the bifunctional urea and the formed oxazolidine [105] intermediate and removal of the autoinduction behavior typically observed in this reaction. (*S*)-3-Thiaproline (20 mol%) was able to catalyze the α-aminoxylation of aldehydes in the presence of water and tetrabutylammonium bromide, giving, after reduction of compounds **97**, the corresponding α-aminoxy alcohols in good yields and enantioselectivities (74–88%, 93–98% ee) [106]. The use of catalyst **14a** (10 mol%) in the presence of a carboxylic acid provided access to the opposite enantiomer *ent*-**97**, as a unique compound, albeit in moderate yields (55–88%, 95–99% ee) [107]. As well as proline derivatives, chiral binaphthyl-based secondary amines have been used as catalyst in this reaction. Thus, the corresponding **72b** ($R^3=CO_2H$, $R^4=3,4,5\text{-}F_3C_6H_2$, 5 mol%) [108] has been applied in the α-aminoxylation of aldehydes, yielding after reduction of compounds **97** the corresponding α-aminoxy alcohols in moderate yields and good enantioselectivities (69–89%, 86–88% ee). When catalyst **72c** (R^3 = NHTf, R^4 = H) was used, the product with the opposite configuration was obtained (49–96%, 97–98% ee). This behavior was ascribed to the different approach of the electrophile to the enamine, directed by the functional groups at the catalysts (carboxy group in **72b** and triflamide in **72c**).



Scheme 27.18

In addition, ketones are suitable substrates for the α-aminoxylation reaction. This transformation was applied to the cyclohexane-1,4-dione monoketal using (*S*)-proline (**21**, 30 mol%) as catalyst in DMF as solvent, affording the oxidation product, which was further transformed into (*R*)-4-hydroxycyclohex-2-enone in 63% yield and 94% ee, which, in turn, has been used extensively as a synthetic building block in organic chemistry. When the reaction was applied to the asymmetric desymmetrization of polysubstituted cyclic meso-ketones, the expected chiral products were obtained in high diastereo- and enantioselectivities [109]. Meanwhile, the desymmetrization of 3-substituted cyclobutanones afforded chiral 4-substituted 5-hydroxy-γ-lactams, through an aminoxylation–cyclization tandem process, with moderate results [110]. Although, the reaction with related acyclic ketones failed, aminoxylated methyl ketones have been prepared by a one-pot tandem aminoxylation of linear, β-branched, β-alkylthio, and ω-oxygenated aldehydes and chemoselective diazomethane homologation. Using nitrosobenzene (**70a**) and (*S*)-proline (**21**, 10 mol%) as catalyst in DMSO at room temperature, the corresponding products were obtained in moderate yields and high enantioselectivities (41–60, 95–99% ee), and this process has been applied to the synthesis of a chiral building block intermediate for the synthesis of epothilones [111]. DFT studies of this process revealed that the reaction was controlled by electrostatic/dipole–dipole interactions [112].

To recover and reuse the catalyst, proline has been supported to a Merrifield-type resin through click chemistry to give a polymeric-supported catalyst (20 mol%) that was used in the α-aminoxylation of cyclic ketones and aldehydes to give the corresponding aminoxylated products in moderate yields (35–89%) and excellent enantioselectivities (96–99% ee) [113]. The insoluble catalyst could be recovered and reused up to three times without a loss in activity and applied in a continuous-flow setup. In addition, (*S*)-proline (**21**, 20 mol%) was reused in the α-aminoxylation of ketones and aldehydes in [bmim]BF_4 as reaction media, giving good results (50–98%, 97–99% ee), with the ionic liquid containing (*S*)-proline being used up to six times without any detrimental effect on the results [114]. The use of imidazolium ion-tagged proline **33** [115] and the related triazolium ion-tagged proline (10 mol%) [116] as catalysts under the same reaction conditions permitted the recovery and reuse of the catalytic system up to six and five times, respectively, affording similar results to those of simple proline. Furthermore, proline was covalently bonded to the natural product isosteviol, giving an amphiphilic catalyst that can be used as in a phosphate buffer solution, providing products **97** in good results (79–96%, 94–99% ee) [117].

The easy detection of the end of the α-aminoxylation reaction catalyzed by (*S*)-proline (**21**) has allowed the *in situ* transformation of compounds **97** into interesting chiral functionalized compounds through the use of tandem one-pot processes [118]. This synthetic strategy has been applied to the formal synthesis of HRV 3C-protease inhibitor (1*R*,2*S*)-thysanone [119], the synthesis of the atorvastatin side chain (a building block present in the statin family that acted as cholesterol regulator) [120], and the synthesis of the lactone moiety of compactin and mevinolin [121].

In addition, several total natural products or drug syntheses [122] were performed following this protocol. For instance, (*S*,*S*)-ethambutol (**23**) [24], (*R*)-selegiline (**24**) [25], and (–)-anisomycin (**27**) [28], which were synthesized by means of an organocatalyzed α-amination reaction, could be obtained with similar results using this reaction. This transformation has been also applied as the key step in the synthesis of the anti-inflammatory halipeptin A (**98**) [123], the antitumor agents tarchonanthuslactone (**99**) [124], (+)-cytotrienin A [125], and (+)-harzialactone A and (*R*)-(+)-4-hexanolide [126], the antiepileptic drug levetiracetam (**100**) [127] and (–)-talampanel [128], the antibacterials linezolid (**101**), eperezolid [129], passifloricin A, verbalactone, and massioalactone [130], the antihypertensive moprolol and other guaifenesin derivatives [131], the pheromones (–)-*endo*-brevicomin (**102**) [132] and (+)-disparlure [133], the enzyme inhibitor (+)-panepophenanthrin (**103**) [134], the β-adrenergic blockers (S)-propranolol (**104**) and (*S*)-naftopidil [135] and the alkaloids conhydrine, sedamine (**105**) [136], coniine, coinicine [137], and antofine [138], among several interesting lactones such as strictifolione [139] and Hagen gland lactones [140] (Figure 27.4).

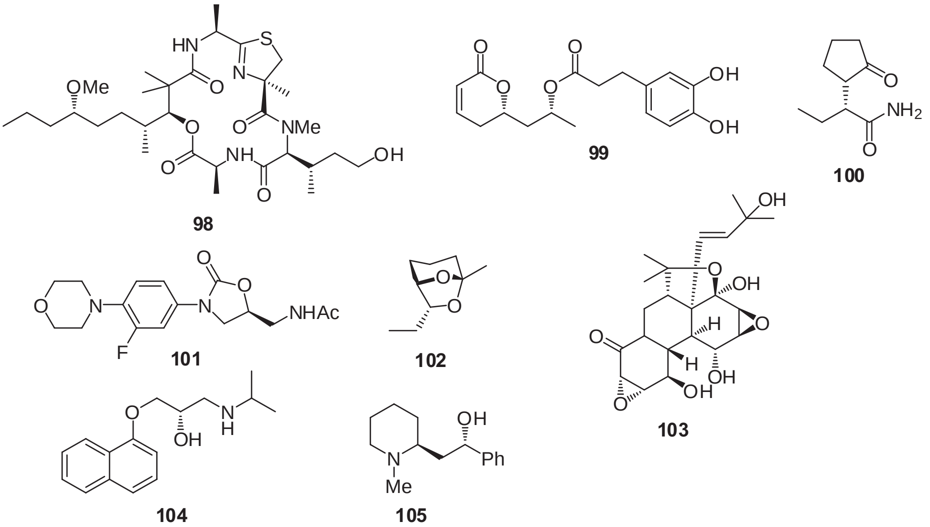


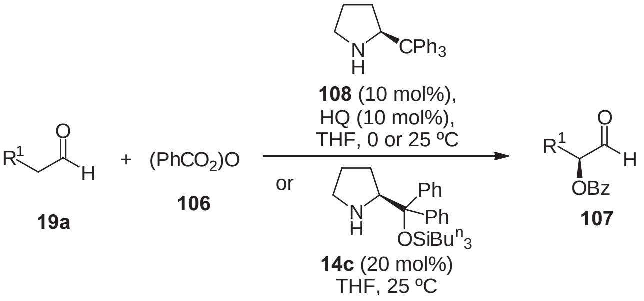
Figure 27.4 Examples of synthesized compounds for which the organocatalyzed α-amination reaction is the key step.

Pyrrolidinyl tetrazole (**36**) [141] was also an efficient catalyst for the sequential or tandem α-aminoxylation of aldehydes, employed in the synthesis of chiral polyfunctionalized compounds [142]. In addition, chiral Brønsted acids were used as catalyst for this reaction. Thus, binaphthyl phosphoric acid derivatives (1 mol%) were applied as catalysts in the α-hydroxylation of cyclic 1,3-dicarbonyl compounds **46** with 4-chloronitrosobenzene (**70c**), affording the corresponding α-hydroxy β-ketoesters in high O/N selectivity (94 : 6) and good yields and enantioselectivities (49–88%, 68–98% ee) [143]. In addition, oxoindoles of type **61** were suitable substrates for the α-oxoamination reaction catalyzed by thiourea derivatives, such as compound **17** (20 mol%) [144], or dimeric cinchona derivative **65** (10 mol%) [145] affording the corresponding 3-hydroxyoxindole derivatives in moderate (54–94% yield, 23–70% ee) or good results (65–86% yield, 73–96% ee), respectively.

27.3.1.4 **Miscellaneous Oxidation Processes**

Other methodologies can be applied for the direct enantioselective organocatalytic α-oxidation of carbonyl compounds [146]. Thus, proline (**21**), pyrrolidinyl tetrazole (**36**), or its α-methyl derivative (30 mol%) catalyzed the oxidation of several aldehydes and cyclohexanone using *trans*-2-(*p*-methoxyphenylsulfonyl)-3-phenyloxaziridine as oxidant [147], with the use of α-methyl substituted derivatives affording the α-oxidized aldehydes with moderate results (23–67% yield, 12–45% ee).

Better results were achieved with benzoyl peroxide (**106**) as oxidant for aldehydes, employing 2-tritylpyrrolidine (**108**, 10 mol%) in the presence of hydroquinone (HQ, 10 mol%) [148] or catalyst **14d** ($R^2 = Bu^n$) [149] (Scheme 27.19). The products **107** were obtained with high enantioselectivities (93–94% and 90–94% ee, respectively). This type of transformation was used as a key step for the synthesis of (–)-6-acetoxy-5-hexadecanolide by means of a tandem α-oxygenation–allylation–RCM strategy mediated by catalyst **14a** [150]. Catalyst **38** (10 mol%) in the presence of 2,6-di-*tert*-butyl-4-methylphenol and trichloroacetic acid (10 mol%) promoted benzoyloxylation of the corresponding ketones, giving the oxidized products in moderate yields (45–81%) and good enantioselectivities



Scheme 27.19

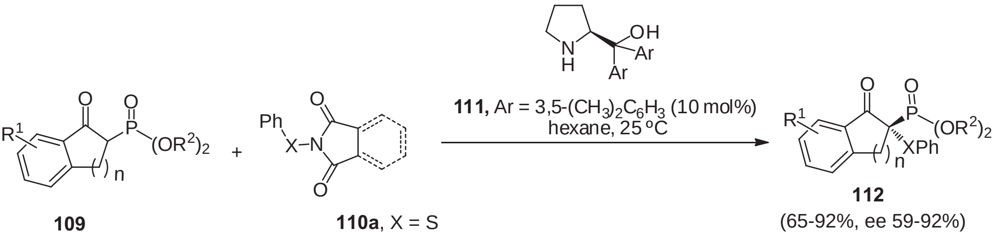
(84–99% ee) [151]. Worse results were achieved in the α-tosylation of ketones using chiral hypervalent iodide reagents in the presence of *m*-chloroperbenzoic acid (ee < 18%) [152].

Molecular oxygen, which is considered as the "greenest oxidant," can also be used for the synthesis of α-hydroxy carbonyl compounds (50–71% yield, 74–98% ee) catalyzed by compound **14a** (R = Me, 20 mol%) in the presence of tetraphenylporphine (1 mol%), in $CHCl_3$ at 0 °C and using ultraviolet light to generate singlet molecular oxygen [153]. Oxoindoles **61** can be oxidized using molecular oxygen as oxidant and under phase-transfer catalysis using cinchonidine catalyst **7b** (R = H, X = Cl, 20 mol%) in the of presence triethyl phosphite [$(EtO)_3P$] and potassium hydroxide as a base, affording the corresponding α-hydroxy 3-substituted oxindole derivatives in 91–99% yield and 67–93% ee [154].

Using a single-electron transfer (SET) reagent, such as iron trichloride and sodium nitrite, the radical α-oxygenation of aldehydes has been accomplished with oxygen as a co-oxidant in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and chiral imidazolidinone of type **86** as the ammonium tetrafluoroborate salt as catalyst, giving the α-oxygenated product in good yields and enantioselectivities (49–80%, 32–90% ee) [155]. This process can also be carried out using an electrochemical oxidation and catalyst **14a** (50 mol%), although modest results were achieved [156]. A metal-free process was accomplished by using benzoyl peroxide (**106**) as oxidant and catalyst **72d** ($R^3 = R^4 = Ph_2CHOSiMe_3$, 5 mol%) to give the corresponding α-oxygenated alcohols, after *in situ* reduction with sodium borohydride, in high yields and enantioselectivities (89–95%, 95–98% ee) [157].

27.3.2
Sulfenylation and Selenenylation Processes

Prolinol derivatives have shown their supremacy in this type of transformation. Thus, the α-sulfenylation of an aldehyde combined with a stereospecific [2,3]-sigmatropic rearrangement organocatalyzed by diarylprolinol **14c** (10 mol%) has provided a useful protocol for the enantioselective synthesis of chiral vinyl glycines, allenamides, and β,γ-unsaturated α-aminophosphonates [158]. Cyclic β-ketoesters **46** were also suitable substrates for the organocatalyzed α-sulfenylation reaction, using prolinol catalyst **111** (20 mol%) and *N*-(phenylthio)phthalimides (**110a**, X = S) to afford the corresponding products in good yields (68–98%) and enantioselectivities (30–97% ee). The scope of this reaction has been extended to the enantioselective sulfenylation of β-keto phosphonates **109** (Scheme 27.20), providing access to chiral products **112** bearing a hetero-quaternary stereocenter [159]. Furthermore, several catalytic domino reactions between α,β-unsaturated aldehydes and *N*-(phenylthio)succinimide (**110a**, X = S) using as catalyst diaryl prolinol **14a** have been reported [160]. 2,5-Disubstituted piperazine-diones are also suitable substrates for the α-sulfenylation reaction, with quinine (10 mol%) providing the best results (27–96% yield, 10–75% ee) for this reaction [161].



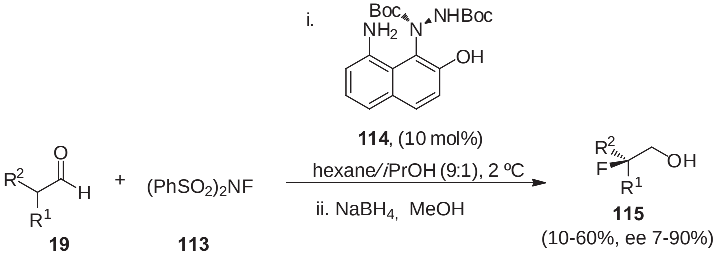
Scheme 27.20

α,α-Diaryl-prolinol catalysts **14c** (5 mol%) in combination with *p*-nitrobenzoic acid or **14a** (20 mol%) were an efficient system to promote the α-selenenylation of a wide range of aldehydes, including alkyl, alkenyl, and hetero-substituted aldehydes, using *N*-(phenylseleno)phthalimides (**110b,** X = Se) as electrophile [162], affording the expected products with excellent enantioselectivities (63–99% yield, 65–99% ee). These α-selenenylated products were further transformed into the corresponding γ-hydroxy-α,β-unsaturated sulfones or esters [163], with this methodology being applied to the formal synthesis of alkaloid (+)-α-conhydrine or to chiral α-alkyl and α-vinyl amino acids by stereospecific [2,3]-sigmatropic rearrangement [164]. Polystyrene-supported proline, prolinamide, or imidazolidinone derivatives [165] have been applied to the α-selenenylation of aldehydes, affording the corresponding α-selenenylated products in high conversions but with low enantioselectivities. These supported catalysts could be reused up to four cycles without losing their activity.

27.4
Enantioselective α-Halogenation of Carbonyl Compounds

Molecules bearing a stereogenic center with a carbon–halogen bond are useful intermediates in organic chemistry, with several organocatalytic reactions being reported to perform this task [166].

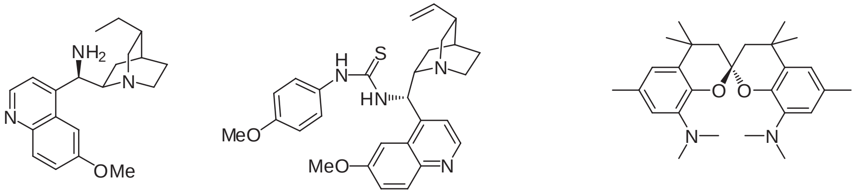
The most extensively studied halogenation process is probably the α-fluorination of carbonylic compounds, due to the unique properties of the fluorinated compounds [167]. Imidazolidinones of type **91** (20 mol%) could be used to promote the α-fluorination of linear aldehydes (**19a,** $R^2 = H$) using *N*-fluorobenzenesulfonimide (NFSI, **113**) as a fluorine source, affording the corresponding fluorinated products in 70–96% yields and with excellent enantiomeric excesses (91–99% ee) [168]. Further transformation of the so-obtained compounds allowed the synthesis of the corresponding β-fluoroamines in good yields (65–82%) and enantioselectivities up to 99%. Chiral β-fluoroamines were also synthesized by a multicomponent organocascade method starting from α,β-unsaturated aldehydes **13** using prolinol **14a** (20 mol%) as catalyst [169]. The use of chiral catalyst **114** (10 mol%) permitted α-fluorination of α-branched aldehydes **19**, using NFSI as fluorine source; the best results in terms of enantioselectivities were achieved when R^1 was an aromatic substituent (Scheme 27.21) [170]. The use of tandem processes involving the organocatalyzed α-fluorination reaction of aldehydes in combination with other synthetic process has allowed the asymmetric synthesis of very interesting chiral fluorine compounds [171].



Scheme 27.21

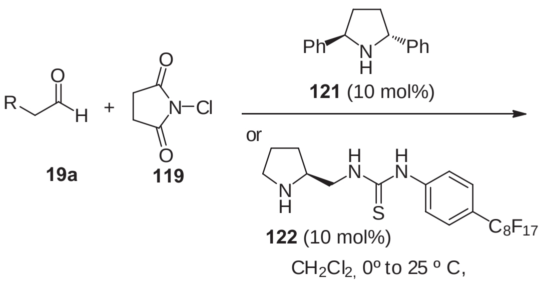
Recently, the direct fluorination of ketones **40**, which was an unsolved problem due to low conversions and enantioselectivities, has been reported [172]. Thus, by using NFSI (**113**) as fluorine source, cinchona alkaloid derivative **116** (10 mol%, Figure 27.5) in the presence of trichloroacetic acid, and sodium carbonate the fluorination of cyclic ketones was promoted with good results (45–88% yield, 88–99% ee). The preparation of chiral α-fluoroketones was also performed with similar results by fluorodesilylation of silyl enol ethers catalyzed by bis-cinchona alkaloid **76** (10 mol%) under similar reaction conditions [173], with this procedure being extended to the enantioselective fluorination of oxoindoles of type **61.** In addition, chiral fluorine-substituted quaternary stereocenters can be obtained (41–96% yield, 48–99% ee) by fluorination of cyclic β-ketoesters **46** using bifunctional thiourea catalyst **117** (20 mol%) [174] or spiro-chiral ammonium salt type **49** (2 mol%) with excellent results (95–99%, 80–98% ee) [175]. Worse results were obtained when using C_2-symmetric catalyst **118** (10 mol%) under similar reaction conditions [176].

The use of diphenylpyrrolidine (**121,** Scheme 27.22) as catalyst for the chlorination of pentanal and undecanal using *N*-chlorosuccinimide (NCS, **119**) provided



116 **117** **118**

Figure 27.5 Organocatalysts used in the fluorination of ketones.



Scheme 27.22

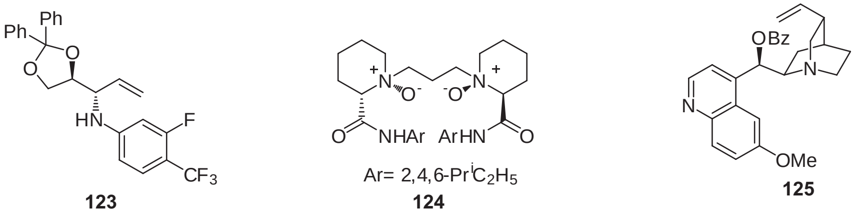
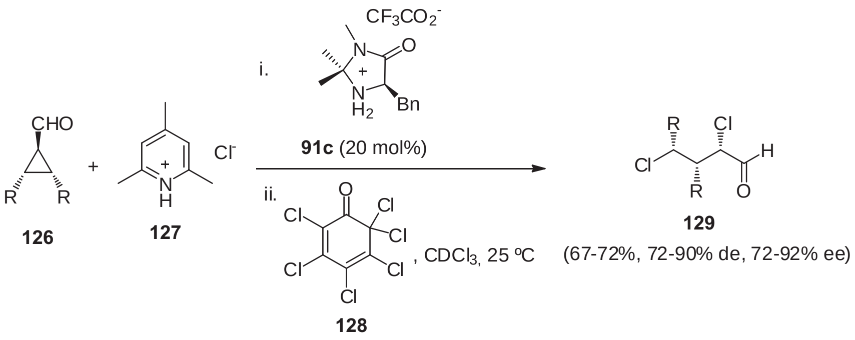


Figure 27.6 Organocatalysts used in the chlorination of cyclic β-ketoesters and oxoindoles.

an excellent method to obtain the corresponding products **120** in high yields and good enantioselectivities (91–97%, 85–89% ee). These chlorinated aldehydes served as starting materials for the synthesis of alkynyl, phenyl, alkyl, and alkenyl epoxides and *N*-alkyl terminal aziridines [177]. Alternatively, imidazolidinone **91b** (20 mol%, $R^3 = Me$) as its trifluoroacetic salt can be used in the same type of process to give chiral epoxides [178]. The use of fluorous pyrrolidine derivative **122** as catalyst led to similar results, with the catalyst being recovered by a fluorous column and reused once more, affording the same results [179].

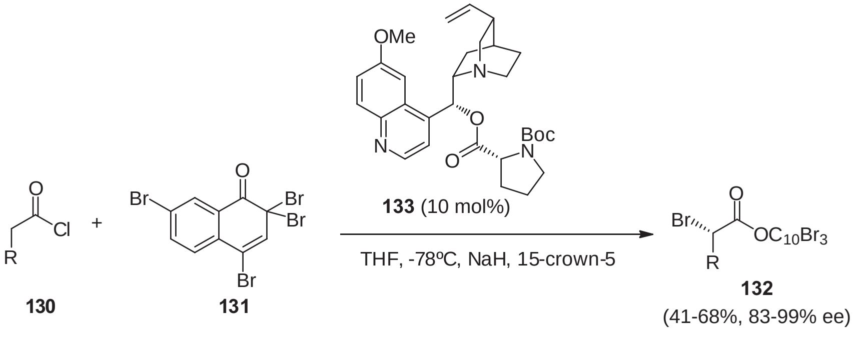
Cyclic β-ketoesters **46** have been chlorinated in nearly quantitative yields using modular chiral amine **123** (10 mol%, Figure 27.6) and NCS as chlorination reagent, providing the corresponding chiral quaternary chlorinated products with up to 92% ee [180]. Under similar reaction conditions, *N,N′*-dioxide catalyst **124** gave better results [181]. However, neither of these catalysts was able to promote efficiently the α-chlorination of acyclic β-ketoesters. Meanwhile, *O*-benzoylated quinidine (**125**, 20 mol%) promoted the chlorination of aryl-oxoindoles **61** in excellent yields (85–99%) and enantioselectivities that were highly dependent on the electronic and steric nature of the substituents on the oxoindoles (7–93% ee) [182].

The enantioselective synthesis of 1,3-dichlorides **129** with good results was performed starting from *meso*-aldehydes **126** by using as catalyst imidazolidinone compound **91c** as its trifluoroacetic salt, and reagents **127** and **128** as Cl^- and Cl^+ sources (Scheme 27.23) [183].



Scheme 27.23

The incorporation of a bromine atom at the α-position of an aldehyde is a well-established procedure, which can be carried out using for instance catalyst **72a** (10 mol%), affording the brominated product with good results (71–94%, 92–99% ee) [184]. This methodology has even been applied to the synthesis of complex molecules by a cascade process [185]. Alternatively, chiral α-bromo carbonyl compounds can be synthesized by the double α-bromination–esterification process depicted in Scheme 27.24, catalyzed by phase-transfer reagent **133**, to give 1,3,6-tribromo-2-naphthyl esters **132** [186] in high enantioselectivities when aliphatic acid chlorides, unsubstituted aryl-acetyl chlorides, or aryl-acetyl chlorides substituted with electron-donating groups were used as substrates. The proposed mechanism of the reaction occurs through the formation of a zwitterionic enolate intermediate by reaction of the acid chloride **130** with the catalyst and the base, abstraction of Br^+ from reagent **131** to give an ion-paired intermediate that undergoes transacylation leading to product **132** along with catalyst regeneration.



Scheme 27.24

The direct asymmetric α-iodination of linear aldehydes **19a** was catalyzed by compound **72e** [5 mol%, $R^3 = R^4 = C(C_6F_5)_2OH$], in the presence of benzoic acid as co-catalyst in diethyl ether at 0 °C, using *N*-iodosuccinimide as a iodinating agent, to afford the corresponding chiral α-iodoaldehydes in moderate isolated yields (30–80%) and with excellent enantioselectivities (90–99% ee) [187].

Several mechanistic studies have investigated the origin of the enantioselectivity of the α-halogenation of carbonyl compounds. DFT calculations showed that the enantioselectivity displayed by catalyst **14** in the α-fluorination reaction, using NFSI as a fluorine source, occurred through a enamine-type intermediate, which was attacked from the less shielded *Si* face, leading to the (*S*) configuration of the chiral product [188]. However, other theoretical work proposes that this process took place via a *trans* enol-catalyst complex reacting with NFSI through a new transition state [189], consisting of simultaneous C–F bond formation between the enol and NFSI via fluorine-shift and H-shift from the oxygen of the enol to the nitrogen of the catalyst. Electrospray ionization mass spectrometry has permitted the interception and characterization of the iminium ion intermediate formed by the reaction of prolinamide and aldehyde in the α-chlorination using *N*-chlorosuccinimide as chlorine source, and also transients involving the presence of such a chlorine atom, which seem to prove the first proposed type of mechanism [190]. Furthermore, a kinetic study has allowed an electrophilicity scale to be established of some α-chlorinating reagents used in organocatalytic processes [191].

27.5
Summary and Conclusions

The direct formation of a stereogenic carbon–heteroatom bond adjacent to a carbonyl functionality using organocatalysis has lead to the synthesis of significantly important chiral compounds without any metal traces in the final products, making this synthetic strategy very attractive for industry and for the general chemical community, especially when using more efficient methodologies such as solvent-free, domino, tandem, or multicomponent processes.

Although there has been significant development of this type of transformation during the recent past, there are still some unreported transformations, such as the α-iodination of ketones. Moreover, improvement of the reaction conditions, especially aiming to reduce catalyst loading and increase catalyst recyclability, would enhance the possibilities of application of these procedures to large-scale synthesis.

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Part II
Nucleophile Addition to C=X Bonds

28

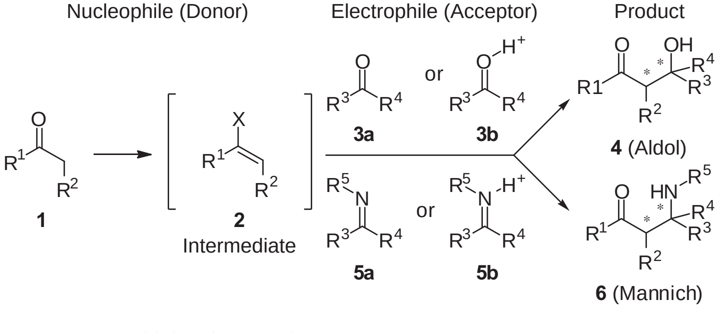
Aldol and Mannich-Type Reactions

Nobuyuki Mase and Carlos F. Barbas III

28.1
Introduction

At the end of the twentieth century, the use of small metal-free organic molecules as organocatalysts in asymmetric bond forming reactions and domino reactions were reported [1]. Organocatalysts allow for the enantioselective synthesis of molecules that were not readily available by traditional methods [2]. Research in this area has advanced rapidly over the past decade, and the versatility, maneuverability, simplicity, and safety of organocatalytic reactions has been demonstrated. This chapter addresses significant achievements in asymmetric syntheses focused on organocatalytic nucleophilic addition to C=O and C=N bonds, namely, aldol and Mannich reactions, covering the literature from 2007 to 2011 [3–7]. The description is subdivided based on various classes of catalysis: enamine, Brønsted acid, hydrogen-bond, Brønsted base, bifunctional, phase transfer, N-heterocyclic carbenes, and supported organocatalysis.

Two carbonyl compounds (**1** and **3**) can combine to form β-hydroxycarbonyl compounds (**4**) in the aldol reaction, discovered by Kane in 1838 [8]. The addition of carbonyl compounds (**1**) to the imine (**5**) to form β-aminocarbonyl compounds (**6**), called the Mannich reaction, was discovered by Marle and Tollens in 1903 (Scheme 28.1) [9]. These synthetically and historically important break-



Scheme 28.1 Aldol and Mannich reactions.

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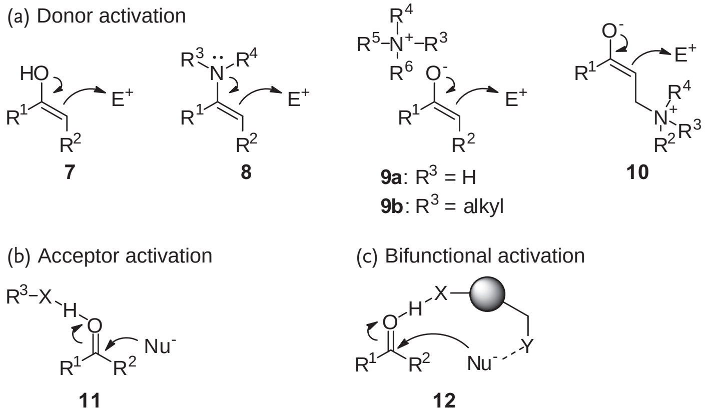


Figure 28.1 Activation modes and reactive intermediates.

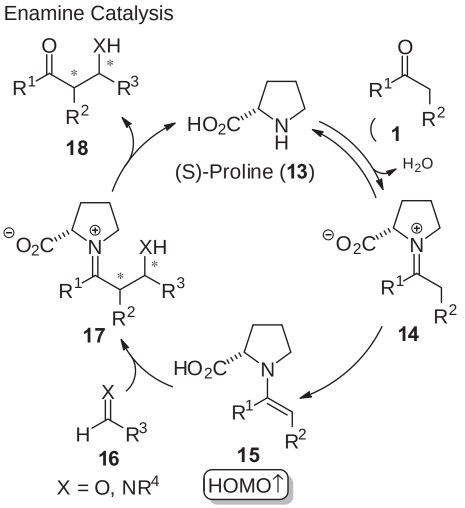
through reactions are among the most fundamental reactions in organic chemistry.

These reactions are classified into three activation modes: (a) donor activation, (b) acceptor activation, and (c) bifunctional activation (Figure 28.1). In donor activation, the carbonyl compounds (**1**) are converted into the nucleophilic enols (**7**) in the presence of acid, which can then attack the protonated reactive carbonyl electrophiles (**3b** or **5b**) through an enol mechanism in Brønsted acid catalysis. The second significant activation mode is called the enamine mechanism. Enamines (**8**), derived by the reaction of the carbonyl compounds (**1**) with a primary or secondary amine followed by loss of H_2O, react with carbonyl electrophiles (**3a** or **5a**) to give the aldol (**4**) or Mannich products (**6**), respectively. The enamine **8** is generally more nucleophilic than the enol **7**, but less nucleophilic than the enolate **9**. The third mode of activation is through the enolate mechanism, in which nucleophilic enolate (**9**) is formed by deprotonation of the α-hydrogen atom of a carbonyl compound (**1**) through Brønsted base catalysis to yield **9a** or in a phase-transfer reaction to yield **9b**. The enolate **10**, derived from addition of nucleophilic catalyst to the α,β-unsaturated carbonyl compound, can react with carbonyl electrophiles (**3**). This activation mode is discussed in detail in Chapter 31 of this book on the Morita–Baylis–Hillman (MBH) and hetero-MBH reactions. Acceptor activation (**11**) through Brønsted acid or hydrogen-bond catalysis is a powerful strategy for carbon–carbon bond formation that is similar to Lewis acid catalysis. The combination of donor and acceptor activation (**12**) is called bifunctional catalysis; in this mechanism, a single organocatalyst simultaneously activates both substrates. In the following sections, based on the activation mode of organocatalysis, significant achievements made employing asymmetric organocatalysts in aldol and Mannich reactions from 2007 to the time of writing will be highlighted.

28.2
Enamine Catalysis

Aldolases are essential, ubiquitous enzymes involved in glycolysis, gluconeogenesis, and the Calvin cycle. They catalyze both carbon–carbon bond formation and cleavage in a stereoselective fashion in the aqueous *in vivo* milieu. For synthetic chemists, aldolases have become useful tools in modern synthetic organic chemistry, in particular in carbohydrate synthesis; for instance, fructose 1,6-diphosphate aldolase (FDP aldolase) converts D-glyceraldehyde 3-phosphate and dihydroxyacetone phosphate into D-fructose-1,6-diphosphate reversibly *in vitro* [10]. Development of type I aldolase-mimicking organocatalysts such as (*S*)-proline (**13**) were discovered through the active research on aldolases and antibodies in 2000 [1, 11].

Aldolase-catalyzed direct aldol reactions and (*S*)-proline-catalyzed reactions occur through the enamine mechanism. An increase in the energy of the HOMO of the enamine intermediate **15** is a key to enhancing the reactivity (Scheme 28.2). The enamine (**15**) attacks an electrophile (**16**) with high stereoselectivity. The catalyst-bound imine **17** is then hydrolyzed, releasing the corresponding product **18** and (*S*)-proline (**13**). The narrow substrate specificity of natural aldolases is vital for life, but not necessarily useful for organic synthesis. Altering the specificity of natural aldolases is relatively difficult and generally requires extensive directed molecular evolution; however, it is easy for synthetic chemists to modify a small organic molecule such as (*S*)-proline. Therefore, enamine catalysis based on (*S*)-proline and its derivatives has been rapidly explored to achieve highly efficient and practical organic syntheses [12].



Scheme 28.2 Aldol and Mannich reactions in enamine catalysis.

28.2.1
Aldol Reactions in Enamine Catalysis

28.2.1.1 Intermolecular Aldol Reactions in Enamine Catalysis

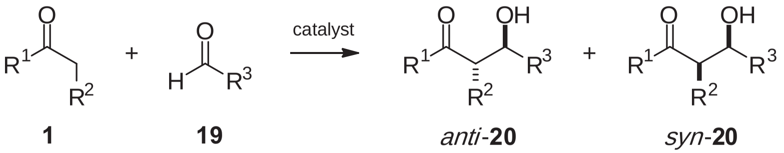
28.2.1.1.1 *Syn*-Selective Aldol Reactions

Chiral 1,2-diols are common structural motifs found in biologically active molecules. Efficient enantioselective syntheses of *anti*-1,2-diols have been developed by using enamine-based organocatalytic strategies, with most research occurring from 2000 to 2006. For example, the aldol reaction employing α-hydroxyacetone (**1**, R^1 = Me, R^2 = OH) as a donor and cyclohexanecarbaldehyde (**19**, R^3 = *c*Hex) as an acceptor provides *anti*-1,2-diol **20** as the major product with enantioselectivities (ee) values up to >99% in the presence of (*S*)-proline (**13**) as a catalyst (Table 28.1, entry 1) [13]. Low reactivity and no diastereoselectivity are observed with dihydroxyacetone (**1**, R^1 = CH_2OH, R^2 = OH) in aqueous media (entry 2) [14], whereas (*S*)-proline catalyzes the aldol reaction between dihydroxy acetone variants such as 2,2-dimethyl-1,3-dioxan-5-one (**1**, R^1 = R^2 = -CH_2OCMe_2O-) and the aldehyde to afford the *anti*-polyol **20** with high enantioselectivity (entry 3) [15].

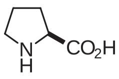
Prior to 2007, there were no reports on the synthesis of *syn*-1,2-diols **20** through an organocatalytic approach; however, use of primary amine-containing amino acid **21** derived from commercially available (*S*)-threonine overcame this synthetically important challenge. An aldol reaction catalyzed by **21** with the unmodified α-hydroxyketone furnishes highly diastereomerically as well as enantiomerically enriched *syn*-1,2-diol **20** in excellent yield (entry 4) [16]. Furthermore, the (*S*)-threonine-based primary amine **21** is a powerful organocatalyst that has been used to synthesize L-rhamnulose and D-fructose derivatives from unprotected or protected dihydroxyacetone as a donor (entries 5 and 6). This new strategy offers organocatalytic mimics of the enzymes L-rhamnulose 1-phosphate aldolase and D-fructose 1,6-diphosphate aldolase [17]. Aldol reactions of linear aliphatic ketones with aldehydes are synthetically important but the regioselectivity and stereoselectivity are difficult to control. The chiral primary–tertiary diamine **22** in combination with *m*-nitrobenzoic acid catalyzes the aldol reaction with high regio-, *syn*-diastereo-, and enantioselectivity (entry 7) [18]. Highly *syn*-selective aldol reactions between aliphatic and aromatic aldehydes are achieved by use of the axially chiral amino sulfonamide **23**, whereas (*S*)-proline (**13**) provides *anti*-selectivity (entry 1 versus 8) [19]. Similarly, axially chiral amino sulfonamide **24** catalyzes the chemo- and stereoselective aldol reaction between aliphatic aldehyde and α-chloroaldehyde (entry 9) [20].

When (*S*)-proline (**13**) is used as a catalyst, the (*E*)-enamine intermediate **26** predominates due to steric interactions in (*Z*)-enamine **25** (Figure 28.2). The *anti*-stereochemistry of the aldol product can be explained by transition state **27**, because the *Si* face of the (*E*)-enamine **26** reacts with *Re* face of the aldehyde. In contrast, with primary amine-containing amino acid **21**, the (*Z*)-enamine **29** of hydroxyketone predominates over (*E*)-enamine **28** due to intramolecular hydrogen bonding and, thus, *syn*-diastereoselectivity has been observed through the bond-forming transition state **30** [16].

Table 28.1 *Syn*-selective aldol reactions.



catalysts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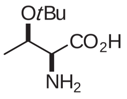
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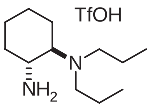
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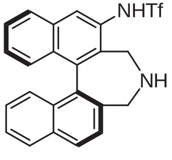
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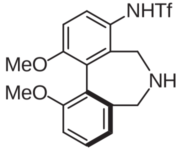
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Entry	R^1	R^2	R^3	Catalyst (mol%)	Conditions	Yield (%)	dr (*anti*:*syn*)	ee (%)[a]	Reference
1	Me	OH	*c*Hex	**13** (20–30)	DMSO, rt, 24–72 h	60	>95:5	>99	[13]
2	CH_2OH	OH	$4\text{-}NO_2C_6H_4$	**13** (20)[b]	PBS (phosphate buffered saline), rt, 24–72 h	Trace	50:50	0	[14]
3	$\text{-}CH_2OCMe_2O\text{-}$		$4\text{-}NO_2C_6H_4$	**13** (20)	DMF, 4 °C, 72 h	89	86:14	93	[15]
4	Me	OH	$4\text{-}NO_2C_6H_4$	**21** (20)	NMP (*N*-methylpyrrolidone), 4 °C, 16–48 h	>95	5:95	98	[16]
5	CH_2OH	OH	$4\text{-}NO_2C_6H_4$	**21** (20)[c]	DMF, rt, 16 h	76[d]	4:96[d]	92[d]	[17a]
6	CH_2OTBS	OTBS	$4\text{-}NO_2C_6H_4$	**21** (20)[e]	NMP, rt, 24 h	85	17:83	93	[17b]
7	Me	Me	$4\text{-}NO_2C_6H_4$	**22** (20)[f]	4 °C, 20–72 h	95[g]	9:91	96	[18]
8	H	Bu	$4\text{-}NO_2C_6H_4$	**23** (5)	NMP, rt, 36 h	77	5:>95	99	[19]
9	H	Bu	[h]	**24** (5)	DMF, rt, 6 h	88[i]	5:>95[i]	98[i]	[20]

a) Enantiomeric excess for the major diastereomer.
b) Sodium dodecyl sulfate (SDS, 10 mol%) was added.
c) 5-Methyl-1*H*-tetrazole (10 mol%) was added.
d) Determined after acetylation.
e) Water (3 vol.%) was added.
f) *m*-Nitrobenzoic acid (10 mol%) was added.
g) Enantiomer of **20** was obtained as a major product.
h) 2-Chloro-3-phenylpropanal was used.
i) Determined after reduction of the aldol product with $LiAlH_4$.

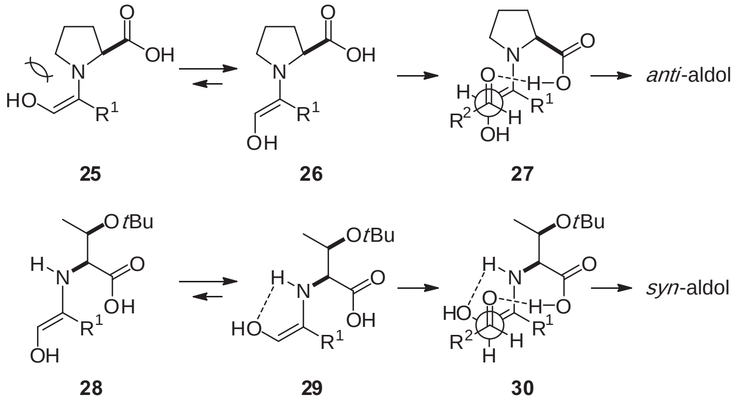
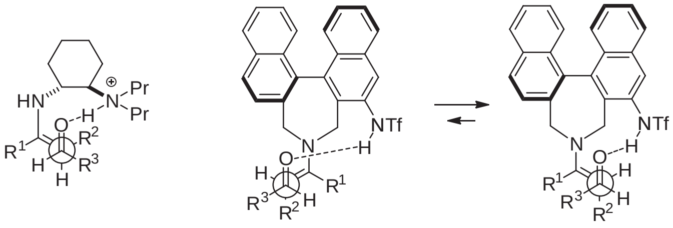


Figure 28.2 Predicted transition state model for *syn*-selective aldol reactions.



31 → *syn*-aldol
R^1 = alkyl

32 → *anti*-aldol
R^1 = H

33 → *syn*-aldol
R^1 = H

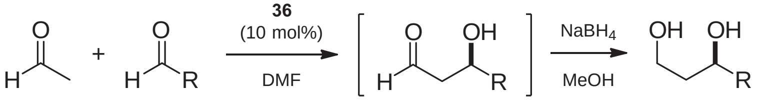
Figure 28.3 Predicted transition state models.

The (*Z*)-enamine transition state **31** was proposed as the intermediate in the *syn*-selective reaction of an acyclic ketone donor with an aldehyde acceptor catalyzed by **22**. In this type of reaction, formation of the (*E*)-enamine of the acyclic ketone is disfavored due to steric repulsion between R^1 and R^2 substituents (Figure 28.3) [18]. The (*E*)-enamine formed by an aldehyde donor with the axially chiral catalyst **23** can react with an aldehyde acceptor that is activated by the proximal acidic proton of **23** via transition model **33**, thus affording the *syn*-aldol product [19].

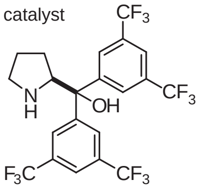
28.2.1.1.2 Aldol Reactions of Acetaldehyde Donor

The commercially available acetaldehyde (**34**) serves as a donor for aldol reactions, but undesirable side products are generally formed because of its very high degree of reactivity. In 2002, the (*S*)-proline catalyzed self-aldol reaction of this acetaldehyde was reported; the reaction yielded over-reacting (+)-(5*S*)-hydroxy-(2*E*)-hexenal with 57 to 90% ee [21]. The synthetically challenging β-hydroxy α-unsubstituted

Table 28.2 Aldol reactions of acetaldehyde donor.



34 **35** **37** **38**



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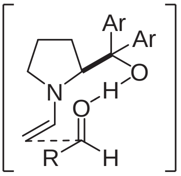


39

Entry	R	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	4-$NO_2C_6H_4$	23	24	85	96
2	2-ClC_6H_4	4	72	85	99
3[a]	Ph	23	120	53	99
4[a]	2-Naphthyl	23	120	50	97
5	4-Pyridyl	23	43	83	99
6	-$CH(OMe)_2$[b]	4	72	92	80

a) Acetaldehyde (5 equiv) was added at 24-h intervals three times.
b) Commercially available aqueous solution (60 wt%) was employed.

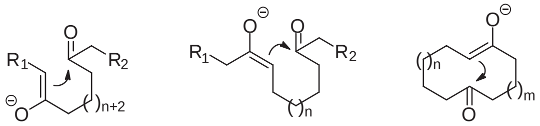
aldehyde **37** is prepared by use of the diarylprolinol **36**; excellent enantioselectivities and moderate to good yields are obtained (Table 28.2) [22]. Reactive acetaldehyde donor **34** forms the enamine intermediate with the catalyst **36**, and the hydroxy group of **36** activates the less reactive aldehyde acceptor **35** to attack the face of the enamine through the transition state **39**.

28.2.1.2 **Intramolecular Aldol Reactions Using Enamine Catalysis**

The intramolecular aldol reaction is an often used approach to the synthesis of cyclic compounds, especially five- and six-membered rings [23]. The two carbonyl components of the substrate react intramolecularly as both electrophiles and as nucleophiles; in addition, they form two different nucleophilic intermediates, namely, *endo* **40** and *exo* **41** aldol (Figure 28.4). Another type of intramolecular reaction is the *transannular* aldol reaction, which may be considered as simultaneously *endo* and *exo*.

28.2.1.2.1 **Intramolecular 6-*Endo* Aldol Reactions**

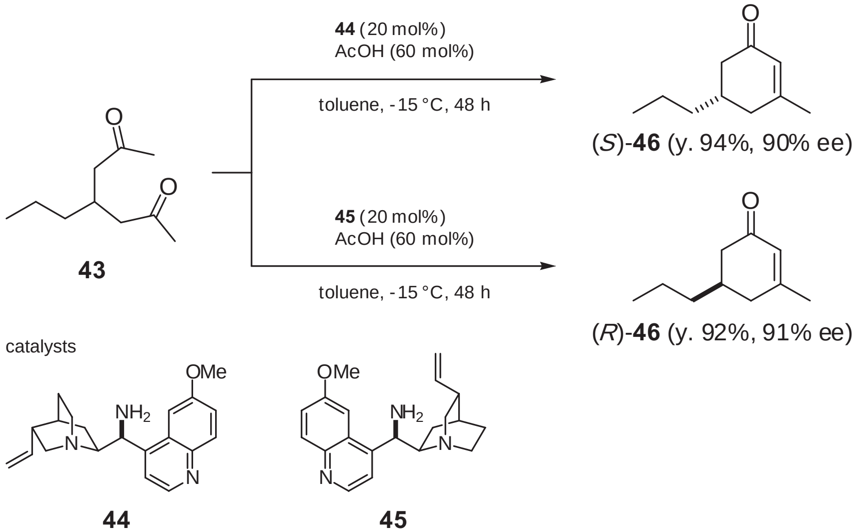
The first example of an organocatalytic enantio-group-differentiating intramolecular 6-*endo* aldol reaction catalyzed by (*S*)-proline was the Hajos–Parrish–Eder–Sauer–Wiechert cyclization [24]. Although impressive, the synthetic scope of the



40 *endo* **41** *exo* **42** *transannular*

Figure 28.4 Intramolecular aldol reactions.

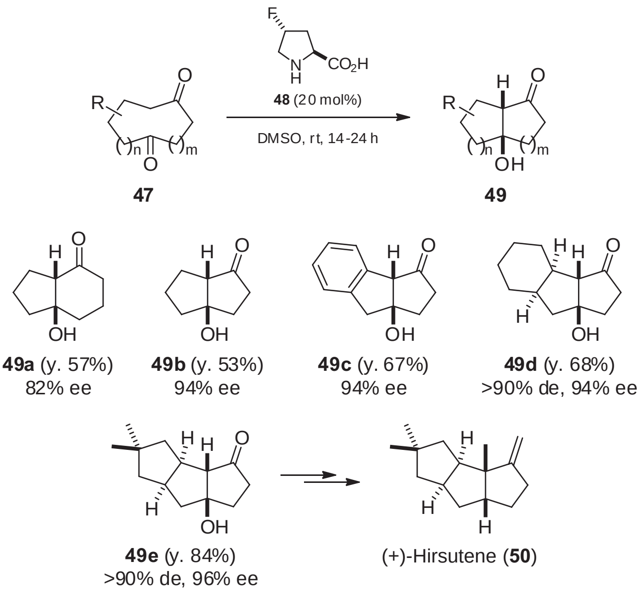
(*S*)-proline-catalyzed reaction is not sufficient; therefore, a large number of (*S*)-proline-derived secondary amine catalysts have been developed. Primary amine catalysts derived from natural amino acids and cinchona alkaloids have also emerged as highly versatile and powerful catalysts [25]. For example, in the intramolecular 6-*endo* aldol reaction of diketone **43**, quinine-derived primary amine **44** in acetic acid affords the cyclic ketone (*S*)-**46** in 94% yield with 90% ee (Scheme 28.3); (*S*)-proline gives the cyclization product in low yield with moderate ee. In addition, the pseudo-enantiomeric quinidine-derived primary amine **45** delivers the opposite product, the (*R*)-enantiomer **46**, with similar yield and enantioselectivity [26].



Scheme 28.3 Intramolecular 6-*endo* aldol reactions.

28.2.1.2.2 Intramolecular *Transannular* Aldol Reactions

Since intramolecular *transannular* aldol reactions create two new rings and at least two new stereogenic centers in a single process, the corresponding cyclic β-hydroxy ketones are useful for the synthesis of polycyclic natural products. The *trans*-4-fluoro proline **48** is superior to (*S*)-proline in catalysis of this type of reaction, affording excellent diastereoselectivity and enantioselectivity (Scheme 28.4). The utility of this reaction has been demonstrated in a total synthesis of (+)-hirustene (**50**), is a fungal metabolite first isolated from the basidiomycete *Coriolus consors* [27].



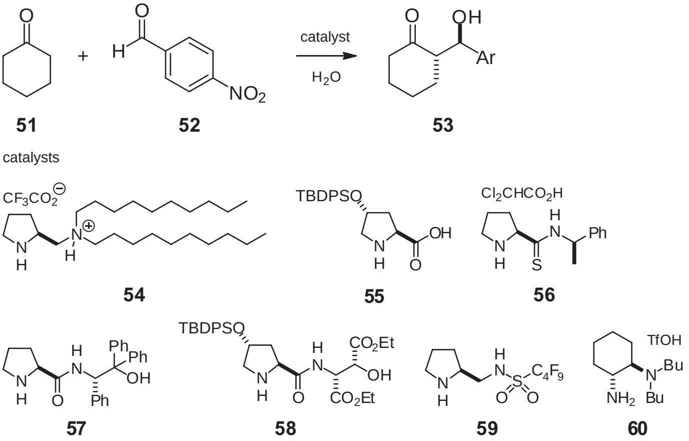
Scheme 28.4 Intramolecular *transannular* aldol reactions.

28.2.1.3 Aldol Reactions in Water, on Water, and by Water

In general, organocatalytic reactions are carried out in a one-pot operation by stirring a carbonyl compound, an amine, and an electrophile in conventional organic solvents, such as DMSO, DMF, or $CHCl_3$, which are toxic, flammable, and volatile. Removal of water is not required for the formation of an enamine intermediate that proceeds to react directly with an electrophile, and water-tolerance is a desirable characteristic for an organocatalyst. Unlike native aldolases or aldolase antibodies, however, in the presence of bulk water aldolase-type organocatalytic reactions generally result in very poor yield and stereoselectivity. It is a common misconception to consider enzymatic reactions as actually taking place "in water." An enzyme-catalyzed reaction might more instructively be regarded as taking place in an organic solvent wherein the enzyme itself is essentially a water-soluble reaction flask that presents a stereo-defined array of organic side-chains that affect catalysis. As noted by the Sharpless group, the use of water as the only supporting medium for a reaction provides for ease of product isolation, high specific heat capacity, high specific inductive capacity, unique redox stability, and non-exhaustible resource, even if the rate acceleration is negligible [28]. Here, we highlight developments in aldol reactions catalyzed by enamine-based organocatalysts in aqueous media without addition of organic solvents [29–31].

Pioneering work in this field has been independently reported based on two distinct strategies. Designed small diamine catalyst **54** (10 mol%) in the presence of trifluoroacetic acid in an emulsion system catalyzes the direct cross-aldol reaction of cyclohexanone (**51**, 2 equiv.) with *p*-nitrobenzaldehyde (**52**) in bulk water (111 equiv.), giving the *anti*-aldol product **53** in quantitative yield with 94% ee

Table 28.3 Aldol reactions in aqueous media without addition of organic solvents.



Entry	Catalyst (mol%)	51 (equiv)	H_2O (equiv)	Temperature (°C)	Time (h)	Yield (%)	dr (*anti*:*syn*)	ee (%)[a]	Reference
1	**54** (10)	2	111	25	24	99	89:11	94	[32a]
2	**54** (10)	1	111	25	48	98	85:15	92	[32a]
3	**54** (1)	2	111	25	24	91	81:19	91	[31a]
4	**54** (0.5)	2	111	25	48	81	81:19	89	[31a]
5	**55** (10)	5	18	Rt	5	86	>95:5	>99	[33a]
6	**55** (1)	2	3	Rt	42	89	94:6	97	[33b]
7	**56** (2.5)	1.2	111[b]	Rt	28	97	93:7	93	[35a]
8	**57** (0.5)	4	55[b]	−10	20–48	NI[c]	87:13	91	[35b]
9	**58** (1)	2	55	25	5	99	>99:1	94	[35c]
10	**59** (10)	10	111	0	9	92	83:17	90	[35d]
11	**60** (10)	2	111	Rt	60	95	95:5	95[d]	[35e]

a) The ee is indicated for the *anti* product.
b) Brine was used as aqueous media.
c) Not indicated in detail.
d) Enantiomer of **53** was obtained as a major product.

(Table 28.3, entry 1) [32a]. A stoichiometric amount of donor was enough to complete the reaction, thereby increasing the economy of the reaction (entry 2). Catalyst loading could also be decreased to 1–0.5 mol% (entries 3 and 4) [31a], although no reaction was observed at 1 mol% catalyst loading using DMSO only as solvent [32b]. Furthermore, crude aldol products are readily isolated by removal of water using centrifugal separation; no extraction and washing are needed. The recovered catalyst **54** as well as water can be used again. The second strategy employed *trans*-L-siloxyproline **55** in a biphasic system (entries 5 and 6) [33]. Since these procedures use a small amount of water (3–18 equiv.), these reactions are generally called “direct aldol reactions in the presence of water” [34a].

A great number of direct aldol reactions in aqueous media with no organic solvent have now been reported. Several of these reports are summarized in Table 28.3 [35]. Based on investigations of different salting-out and salting-in conditions, brine is clearly a unique aqueous media that accelerates the rate of reaction and affects the stereochemical outcome of the aldol reactions due to hydrophobic aggregation (entries 7 and 8).

Since two electron-withdrawing ester groups strengthen the double hydrogen bonds and the siloxy group increases hydrophobicity, catalyst **58** is highly reactive (Table 28.3, entry 9). A combination of fluorous separations with catalysis in water is achieved by the fluorous pyrrolidine sulfonamide **59**, which provides the aldol product **53** in good yield with high stereoselectivity (entry 10). Fluorous extraction allows catalyst recovery and reuse for at least seven cycles. The primary–tertiary diamine **60** in the presence of TfOH also catalyzes the aldol reaction in water (entry 11).

Remarkable temperature-dependent properties were reported for an aqueous aldol reaction using the designed diamine catalyst **54** [31a]. When the direct aldol reaction is carried out in DMSO at 10 mol% catalyst loading, the enantioselectivity sharply decreases as the temperature is raised (Figure 28.5). This observation, that ee decreases with increasing temperature, is quite general for

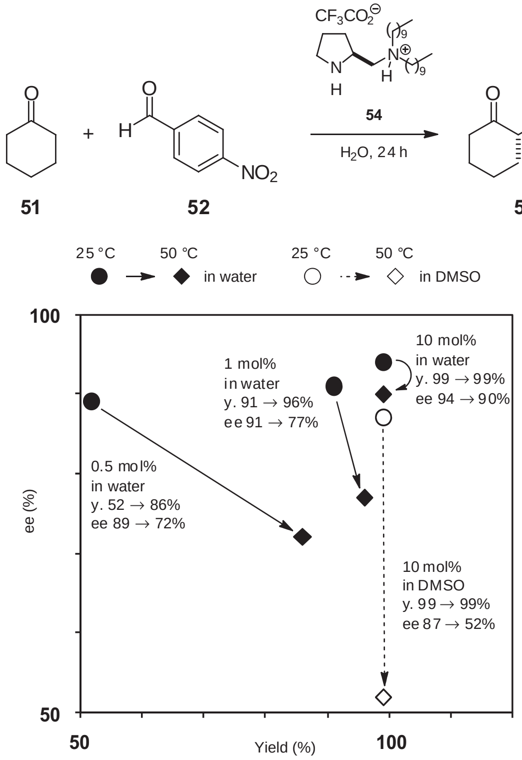


Figure 28.5 Temperature-dependent properties of aqueous aldol reactions.

asymmetric syntheses in organic solvents. On the other hand, with water as solvent, the enantioselectivity is only slightly decreased at elevated temperature and 10 mol% catalyst loading (94 → 90% ee). At 0.5 mol%, reactivity is improved and enantioselectivity is maintained (yield 52 → 86%, ee 89 → 72%). These results suggest that hydrophobic interactions play an important role in reactivity and enantioselectivity, since increased temperature (i.e., entropy) leads to an increased hydrophobic effect.

The mechanism underlying the rate acceleration and the excellent enantioselectivity of reactions catalyzed by **54** in water is complex; a likely "in water" mechanism is shown in Figure 28.6a [31a, 32b, 36]. A liquid organic donor assembles in water due to hydrophobic interactions, which forms a metastable micelle with the catalyst **54**. Aggregation of the organic molecules excludes water from the organic phase and drives the equilibrium towards enamine formation. The enamine intermediate, composed of the carbonyl donor and the catalyst **54**, is more hydrophobic than catalyst **54** alone, therefore the enamine intermediate moves into the organic phase. It is believed that carbon–carbon bond formation between the enamine intermediate and the aldehyde acceptor occurs quickly in the highly concentrated organic micellular phase through a transition state similar to that observed in organic solvents, and then hydrolysis of the enamine intermediate proceeds. An "on water" mechanism has also been proposed [37]. In this mechanism, a free hydroxy group at the oil–water phase boundary protrudes into the organic phase to catalyze reactions via the formation of hydrogen bonds to a donor, an acceptor, and/or the catalyst (Figure 28.6b).

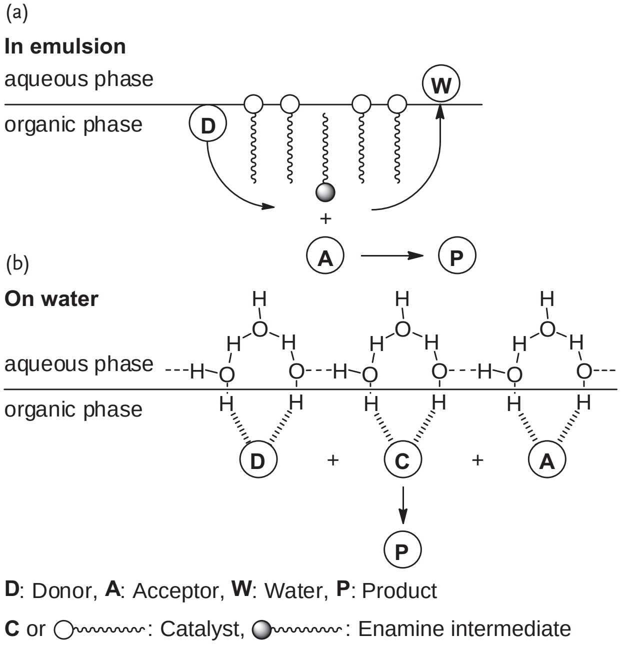
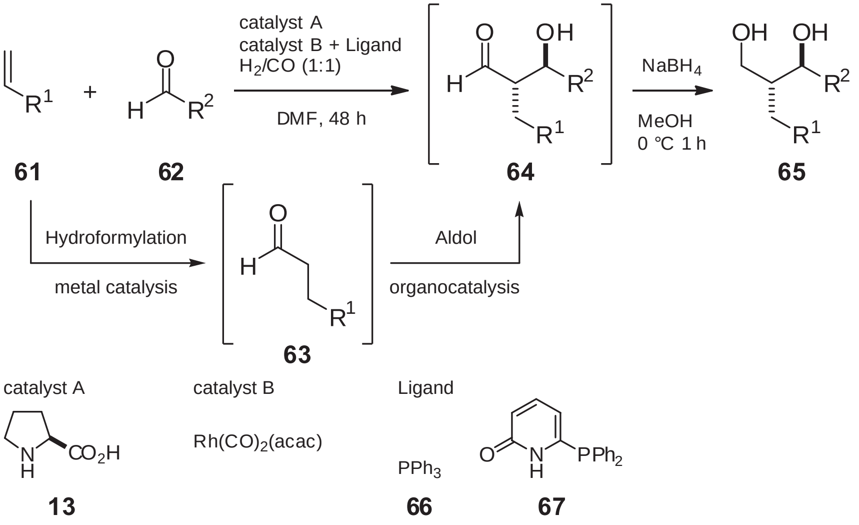


Figure 28.6 Cartoons of (a) in emulsion and (b) on water catalysis.

Table 28.4 Metal-catalyzed and organocatalytic reaction sequence.



Entry	R^1	R^2	13 (mol%)	[Rh] (mol%)	Ligand (mol%)	Conditions	Yield (%)	dr (*anti*:*syn*)	ee (%)[a]
1	H	Pr^i	6	0.2	**66** (4.4)	30 bar, 5 °C	76	95:5	98
2	H	*c*Hex	5	0.25	**66** (5.0)	30 bar, 5 °C	81	93:7	99
3	H	Ph	5	0.25	**67** (1.0)	30 bar, 5 °C	91	75:25	94
4	Hex	Pr^i	0.15	0.01	**67** (0.1)	20 bar, 15 → 5 °C	86	95:5	97

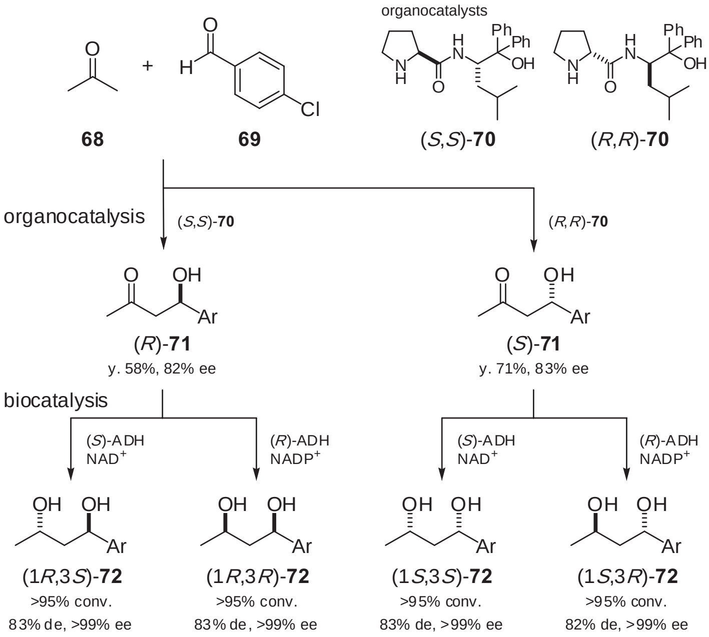
a) The ee is indicated for the *anti* product.

28.2.1.4 Metal-Catalyzed and Organocatalytic Reaction Sequences

In recent years, combinations of transition metal catalysis and organocatalysis have attracted increasing attention in synthetic organic chemistry. These combinations allow for the regio- and stereoselective synthesis of complex molecules from readily available, simple starting materials [38]. A domino Rh complex-catalyzed hydroformylation, following a (*S*)-proline-catalyzed enantioselective cross-aldol reaction sequence is one example (Table 28.4) [39]. Simple alkenes (**61**) are transformed *in situ* into aliphatic aldehydes (**63**), giving aldol products (**64**) in good yields with excellent stereoselectivities in a one-pot operation.

28.2.1.5 Organocatalytic and Biocatalytic Reaction Sequences

Like combinations of metal- and organocatalysts, combining biocatalysis and organocatalysis is a powerful strategy by which to improve the synthetic efficiency. A sequential two-step synthesis based on the organocatalytic aldol reaction and biocatalytic reduction leads to all four possible stereoisomers of 1,3-diols **72** in enantiomerically pure form (Scheme 28.5). The stereochemistry depends on the combination of the organocatalyst **70** and alcohol dehydrogenase (ADH).



conditions: organocatalyst **70** (5 mol%), rt, 18 h
biocatalyst, 2-PrOH, Buffer, rt, 18-67 h

Scheme 28.5 Organocatalytic and biocatalytic reaction sequence.

Furthermore, conversion is improved up to 80% by sequential one-pot synthesis without the work-up step after the organocatalytic aldol reaction [40].

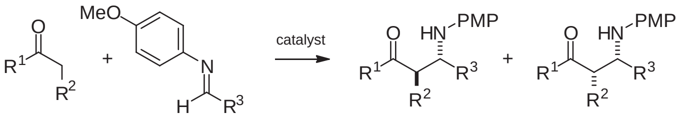
28.2.2
Mannich Reactions in Enamine Catalysis

28.2.2.1 *Anti*-Selective Mannich Reactions

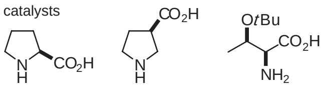
Chiral β-amino carbonyl compounds and 1,2-amino alcohols are among the most valuable building blocks for asymmetric synthesis and catalysis. Efficient enantioselective syntheses of these compounds were reported from 2000 to 2006 using enamine-based organocatalysts. For example, Mannich reactions employing aliphatic aldehyde as a donor with α-imino glyoxylate as an acceptor provide *syn*-adducts (**74**) as the major product with excellent enantiomeric excess in the presence of (*S*)-proline (**13**) as a catalyst (Table 28.5, entry 1) [41]. When the ketone is employed as a donor, the *syn*-isomer is obtained with excellent diastereo-and enantioselectivities (entry 2) [42].

Anti-selective Mannich reactions have been developed using (*R*)-3-pyrrolidine-carboxylic acid (**75**) or primary amine-containing amino acid **21**; these catalysts were designed through consideration of mechanism and transition state models.

Table 28.5 *Anti*-selective Mannich reactions.



1 **73** *anti*-**74** *syn*-**74**



13 **75** **21**

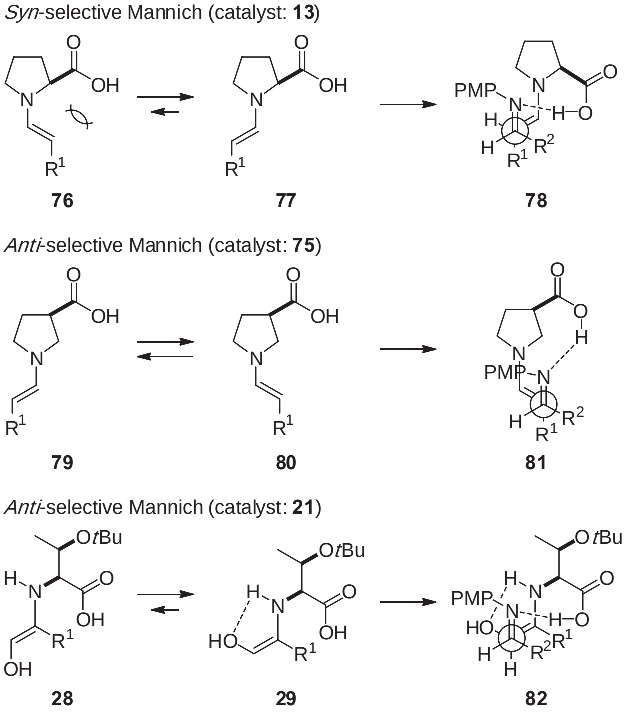
Entry	R^1	R^2	R^3	Catalyst (mol%)	Conditions	Yield (%)	dr (*anti* : *syn*)	ee (%)[a]	Reference
1	H	Pr^i	CO_2Et	**13** (5)	Dioxane, rt, 2–24h	81	5:95	93	[41]
2	Et	Me	CO_2Et	**13** (20)	DMSO, rt, 2–24h	47	5:>95	>99	[42]
3	H	Pr^i	CO_2Et	**75** (5)	DMSO, rt, 4h	81	99:1	94	[43]
4	Et	Me	CO_2Et	**75** (10)	2-PrOH, rt, 20h	91	97:3	97	[43]
5	Me	OH	$4\text{-}NO_2C_6H_4$	**21** (30)	DMSO, 25°C, 22h	85	89:11	94	[16]
6	Me	OH	$4\text{-}NO_2C_6H_4$[b]	**21** (20)	NMP, 4°C	85	94:6	98	[16]

a) Enantiomeric excess for the major diastereomer.

b) Imine **73** was formed *in situ*.

The Mannich reaction of the aldehyde or ketone with α-imino esters catalyzed by **75** under mild conditions affords *anti*-Mannich products (**74**) with high diastereo- and enantioselectivities (Table 28.5, entries 3 and 4) [43]. Furthermore, chiral *anti*-1,2-amino alcohols (**74**) are synthesized through a Mannich reaction between the unmodified α-hydroxyketone **1** (R^1 = Me, R^2 = OH) and imine **73** in the presence of **21** (entries 5 and 6) [16].

With (*S*)-proline (**13**), the s-*trans*-(*E*)-enamine **77** predominates due to steric interactions in *s-cis*-(*E*)-enamine **76** (Scheme 28.6). Position matching between the nucleophilic carbon of the enamine and the electrophilic carbon of the imine controls the stereoselectivity. The *Re* face of the enamine reacts with the *Si* face of the imine through the transition model **78** to afford *syn*-Mannich products. On the other hand, 3-pyrrolidinecarboxylic acid (**75**) gives *anti*-Mannich products, as mentioned above, though the free energy difference between the enamine intermediates **79** and **80** derived from the aldehyde with the catalyst **75** might be similar. From the evaluation of a series of pyrrolidine-based catalysts, the acid group at the β-position of the pyrrolidine ring of the catalyst **75** plays an important role in the *anti*-selectivity of carbon–carbon bond formation. The nucleophilic carbon of enamine **80** is likely to be properly positioned for the reaction with the electrophilic carbon of the imine through the transition state **81** (Scheme 28.6), whereas enamine **79** is too far from the imine to form the bond [43]. With primary amine-containing amino acid **21**, the (*Z*)-enamine **29** of the hydroxyketone predominates over the (*E*)-enamine **28** due to intramolecular hydrogen bonding and, thus, *anti*-diastereoselectivity has been observed through the bond-forming transition state **82** [16].

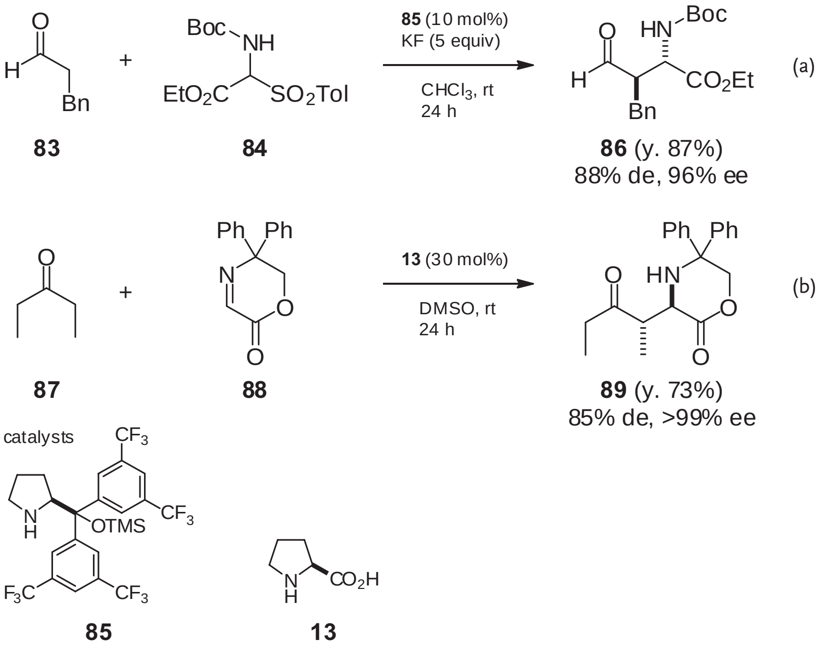

Syn-selective Mannich (catalyst: **13**)

Anti-selective Mannich (catalyst: **75**)

Anti-selective Mannich (catalyst: **21**)

Scheme 28.6 Predicted transition models for *anti*-selective Mannich reactions.

Substrate control is another approach for synthesis of *anti*-Mannich products. The proline-catalyzed Mannich reaction between aldehydes and pre-formed N-Boc-imines affords the *syn*-Mannich product with exceptionally high diastereoselectivities and enantioselectivities [44]. In contrast, the reaction of aldehyde **83** with *N*-Boc-imines, generated *in situ* from the stable α-amido sulfone **84**, catalyzed by the commercially available chiral secondary amine **85** provides *anti*-Mannich product **86** with 96% ee (Scheme 28.7a) [45]. Cyclic iminoglyoxylate **88**, readily prepared from commercially available starting materials, is a useful alternative imine electrophile; its configuration is locked in the (*Z*)-form. Because of the (*Z*)-configuration of imine **88**, the *anti*-selective Mannich reaction proceeds (Scheme 28.7b) [46].



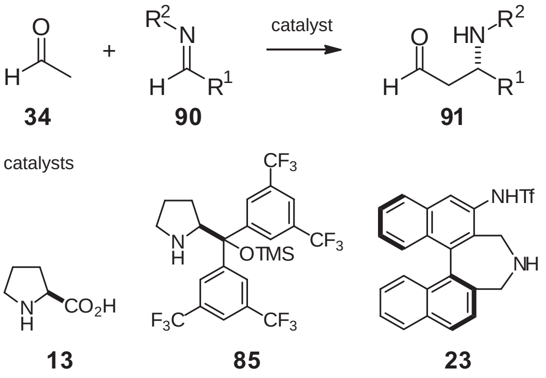
Scheme 28.7 Substrate-controlled *anti*-selective Mannich reactions.

28.2.2.2 Mannich Reactions of Acetaldehyde Donors

Acetaldehyde **34**, which is the simplest of all enolizable carbonyl compounds but highly reactive as an electrophile, is an inexpensive and versatile two-carbon nucleophile in enamine-based Mannich reactions. Mannich reactions of acetaldehyde as a donor with aryl or alkyl substituted *N*-Boc-imines **90** are effectively catalyzed by (*S*)-proline (**13**) in moderate yield but excellent enantioselectivity (Table 28.6, entries 1 and 2) [47]. Chemical yields are improved up to 87% when *N*-benzoyl (Bz)-imine is employed in the presence of diaryl prolinol silyl ether **85** with *p*-nitrobenzoic acid (entry 3) [48]. To suppress side reactions, such as self-aldol reactions, the moderate nucleophilicity of the axially chiral amino sulfonamide **23** is particularly useful for this type of Mannich reaction; these conditions give the corresponding adducts **91** in good yield and excellent stereoselectivity (entries 4 and 5) [49].

α-Monosubstituted Mannich product **93** can form a reactive enamine intermediate with amine catalysts. This intermediate can then react with the other imine electrophiles in what is known as a double Mannich reaction. The Mannich reaction between acetaldehyde (**34**) and three equivalents of *N*-Boc-imine **92** is catalyzed by (*S*)-proline to furnish the double Mannich product **94** in quantitative yield with over >98% diastereoselectivity and 99.98% ee (Scheme 28.8). Cross double Mannich reactions of acetaldehyde with two different imines have also been achieved [50].

Table 28.6 Mannich reactions of acetaldehyde donors.

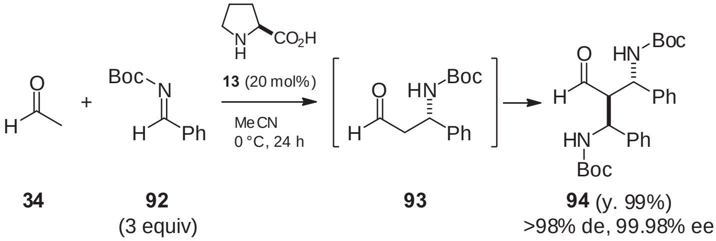


Entry	R^1	R^2	Catalyst (mol%)	Conditions	Yield (%)	ee (%)	Reference
1	Ph	Boc	**13** (20)	MeCN, 0 °C, 2–3 h	54	>98	[47]
2	Bu^i	Boc	**13** (20)	MeCN, 0 °C, 2–3 h	55	>98	[47]
3	Ph	Bz	**85** (10)$^{a)}$	THF, 4 °C, 72 h	87$^{b)}$	97$^{b)}$	[48]
4	Ph	Boc	**23** (2)	0 °C, 4 h	87	99	[49]
5	*c*Hex	Boc	**23** (2)	THF, 0 °C, 4 h$^{c)}$	70	99	[49]

a) *p*-Nitrobenzoic acid (10 mol%) was added.

b) Yield and enantiomeric excess were determined after *in situ* reduction to the corresponding alcohol.

c) The *N*-Boc-protected imine was added by syringe pump over 0.5 h; stirring was then continued for 3 h.



Scheme 28.8 Double Mannich reaction of acetaldehyde with imine.

28.3
Brønsted Acid Catalysis Including Hydrogen-Bond Catalysis

Asymmetric reactions catalyzed by chiral Brønsted acids have became the subject of cutting-edge research in synthetic organic chemistry in recent years [51]. In general, activation of the substrate is enabled via hydrogen bonding or formation of ion pairs, depending on the acidic strength of the catalyst such as phosphoric

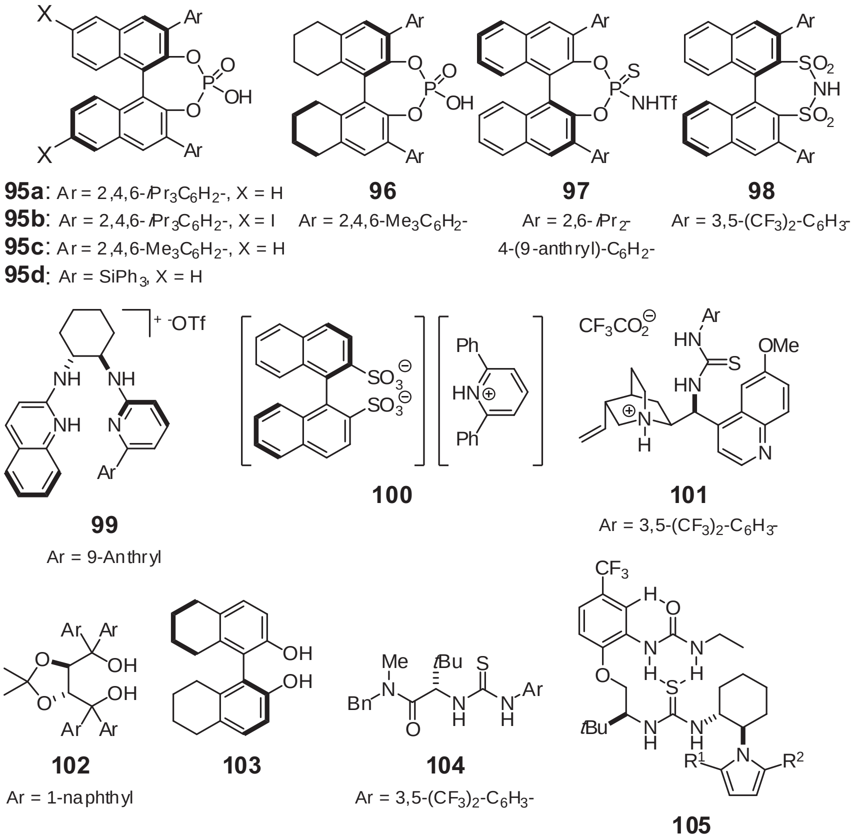

95a: Ar = 2,4,6-iPr$_3$C$_6$H$_2$-, X = H
95b: Ar = 2,4,6-iPr$_3$C$_6$H$_2$-, X = I
95c: Ar = 2,4,6-Me$_3$C$_6$H$_2$-, X = H
95d: Ar = SiPh$_3$, X = H
96
Ar = 2,4,6-Me$_3$C$_6$H$_2$-
97
Ar = 2,6-iPr$_2$-4-(9-anthryl)-C$_6$H$_2$-
98
Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-
99
Ar = 9-Anthryl
100
101
Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-
102
Ar = 1-naphthyl
103
104
Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-
105

Figure 28.7 Representative Brønsted acid and hydrogen-bond catalysts.

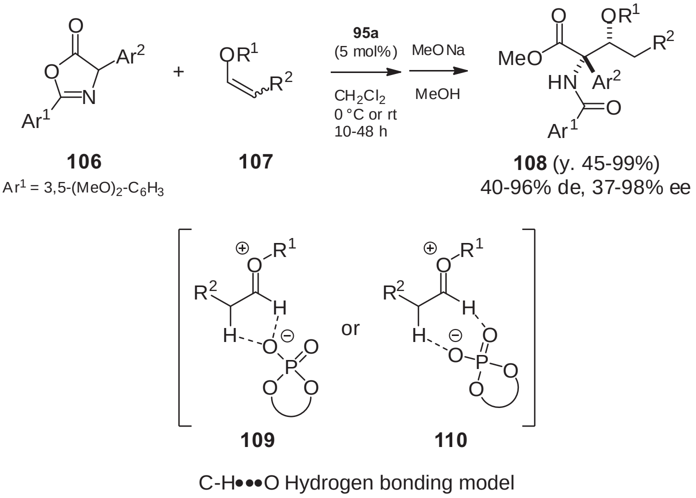
acids [52], ammonium salts, thioureas [53], diols [54], and squaramides [55]. Among the different chiral Brønsted acids (Figure 28.7), axial chiral phosphoric acid derivatives have shown astonishing versatility.

28.3.1
Aldol Reactions in Brønsted Acid and Hydrogen-Bond Catalysis

28.3.1.1 Intermolecular Aldol Reactions in Brønsted Acid and Hydrogen-Bond Catalysis

28.3.1.1.1 Aldol-Type Reactions of Azlactone

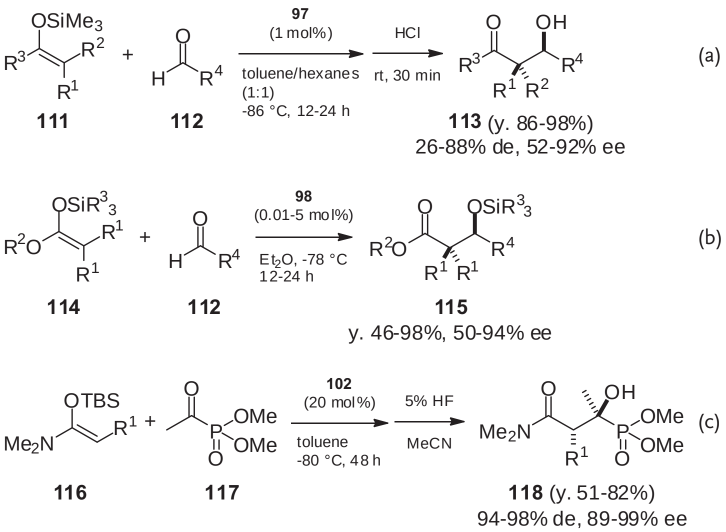
The direct aldol-type reaction of azlactone **106** with an oxocarbenium ion via a protonation of vinyl ethers (**107**) by the chiral phosphoric acid **95a** as a catalyst provides β-alkoxy-α-amino acid derivatives (**108**) bearing a quaternary stereogenic center with high diastereo- and enantioselectivity (Scheme 28.9). The ion pairs **109** or **110** likely have a three-dimensionally-oriented specific interaction between a chiral conjugate base and an oxocarbenium ion, controlling the enantioselectivity of the transformations [56].



Scheme 28.9 Direct aldol-type reactions of azlactone.

28.3.1.1.2 **Mukaiyama Aldol Reactions in Brønsted Acid Catalysis**

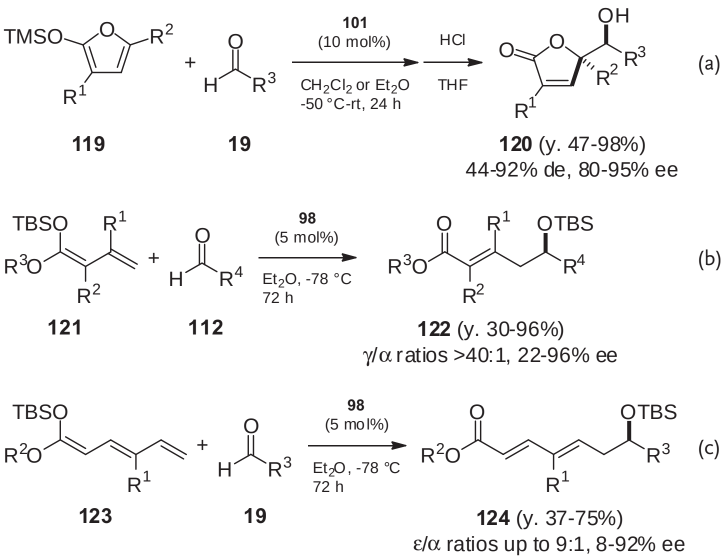
The Mukaiyama aldol reaction is one of the most synthetically reliable carbon–carbon bond forming reactions. Although a wide variety of Lewis acid and Lewis base catalysts have been developed for enantioselective Mukaiyama aldol reactions involving silyl enol ether as a stable enolate component, very few examples of chiral Brønsted acid-catalyzed Mukaiyama aldol reactions were reported before 2006. The catalyst loading (10 mol%) may not be sufficient due to their lower acidities [57]. To increase the reactivities of chiral phosphoric acid catalysts, chiral *N*-triflyl thiophosphoramide **97** was developed to catalyze the Mukaiyama aldol reactions of aldehydes (**112**) using silyl enol ethers of ketones (**111**) as nucleophiles (Scheme 28.10a). From mechanistic studies, the type of catalysis depends on reaction temperature: (i) a Lewis acid pathway associated with the silylated Brønsted acid occurs at room temperature and (ii) a Brønsted acid pathway associated with the Brønsted acid itself takes place at low temperature [58]. A designed chiral disulfonimide **98** was developed as a powerful Brønsted acid for the Mukaiyama aldol reaction of aldehydes using silyl enol ethers of esters (**114**) as nucleophiles; these reactions provide the desired aldol products (**115**) with over 90% ee in most cases (Scheme 28.10b). The actual catalyst is proposed to be an *in situ* generated *N*-silyl imide [59]. A simple chiral diol of TADDOL (α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol) catalyzes Mukaiyama aldol reactions between aldehydes and silyl enol ethers of amides (**116**) [57b]. Hydrogen-bond activation by the diol catalyst **102** is applicable for the Mukaiyama aldol reactions of acyl phosphonates (**117**) with amides (**116**), giving the aldol product **118** with one tertiary and one quaternary stereocenter with excellent diastereo- and enantioselectivity (Scheme 28.10c) [60].



Scheme 28.10 Mukaiyama aldol reactions.

28.3.1.1.3 Vinylogous Mukaiyama Aldol Reactions in Brønsted Acid Catalysis

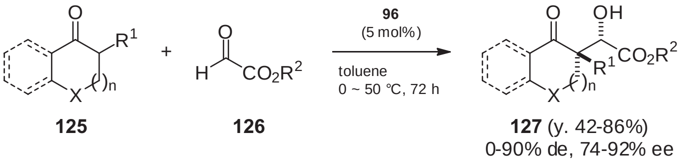
The applications of aldol reactions with α,β-unsaturated carbonyl compounds as nucleophiles, in general called vinylogous aldol reactions, have attracted much attention [61]. Since hydrogen-bond catalysis by TADDOL was extended to the vinylogous Mukaiyama aldol reaction in 2005 [62], organocatalytic approaches using a wide variety of Brønsted acids and hydrogen-bond catalysts have been intensively investigated [63]. The silyloxy furans (**119**) are good substrates for the vinylogous Mukaiyama aldol reaction; however, their applications have been limited until recently. Carboxylate-ammonium salt **101** prepared from a cinchona-thiourea and trifluoroacetic acid is an effective catalyst for the vinylogous aldol reaction of silyloxy furans (**119**) with aldehydes (**19**), producing *anti*-aldol products (**120**) with high enantiomeric excess (Scheme 28.11a) [64]. Like the Mukaiyama aldol reaction (Scheme 28.10b), the vinylogous Mukaiyama aldol reactions of crotonic acid-derived nucleophiles (**121**) with aldehydes (**112**) is catalyzed by the disulfonimide **98**. Extremely high regioselectivities in γ : α ratios up to >40 : 1 and over 90% enantiomeric excesses are observed in most cases (Scheme 28.11b). This methodology was further expanded to ε-selective double vinylogous Mukaiyama aldol reactions (Scheme 28.11c) [65]. The single-step syntheses of chiral α,β- and α,β,γ,δ-unsaturated esters via vinylogous and double vinylogous Mukaiyama aldol reactions would be potentially useful for natural product synthesis.



Scheme 28.11 Vinylogous Mukaiyama aldol reactions.

28.3.1.1.4 Direct Aldol Reactions in Brønsted Acid Catalysis

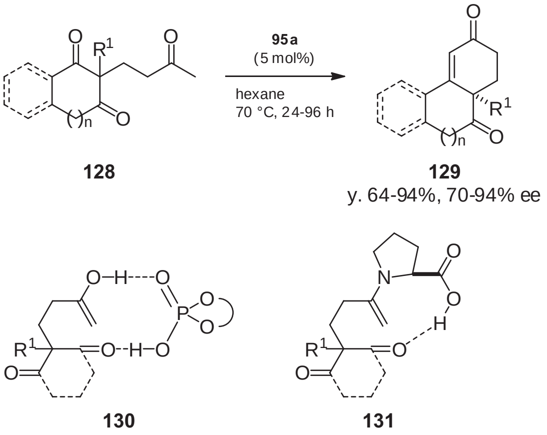
The Mukaiyama aldol reaction is beyond doubt a brilliant triumph of modern synthetic organic chemistry; however, the reaction products are contaminated with pre-activated silyl enol ethers derived from the carbonyl compounds with stoichiometric amounts of silylation agent and base. In addition, silylated wastes are inherently formed. Circumventing the pre-activation process improves atom efficiency; in this case, the carbonyl nucleophiles react directly with the carbonyl electrophiles in the presence of catalyst. The first Brønsted acid-catalyzed direct aldol reactions have been achieved using chiral H_8-BINOL-derived phosphoric acid **96** (Scheme 28.12) [66]. The aldol products (**127**) have *syn*-configurations and, thus, this reaction is complementary to (*S*)-proline catalysis in Brønsted acids, which in general yields the *anti* configuration [11].



Scheme 28.12 Phosphoric acid-catalyzed direct aldol reactions.

28.3.1.2 Intramolecular Aldol Reactions in Brønsted Acid Catalysis

Significant desymmetrizations of *meso*-1,3-diones (**128**) result from intramolecular aldol reactions catalyzed by chiral phosphoric acid **95a**. This method affords a wide variety of chiral cyclohexenones (**129**) in high yields and with excellent enantioselectivities (Scheme 28.13). ONIOM (B3LYP/6-31G*: HF/3-21G) calculations suggest the identity of the reaction intermediate and the origin of the enantioselectivity. In the transition state model **130**, the carbonyl and enol groups are activated by chiral phosphoric acid **95a** with Brønsted acidic and Lewis basic sites, respectively. The attack from the *Si* face is more favorable than attack from the *Re* face and provides the (*R*)-isomer **129** (R^1 = Me) [67]. Since the (*S*)-isomer is formed in the (*S*)-proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert cyclization through transition state **131** [24], Brønsted acid catalysis and enamine catalysis are complementary methodologies.



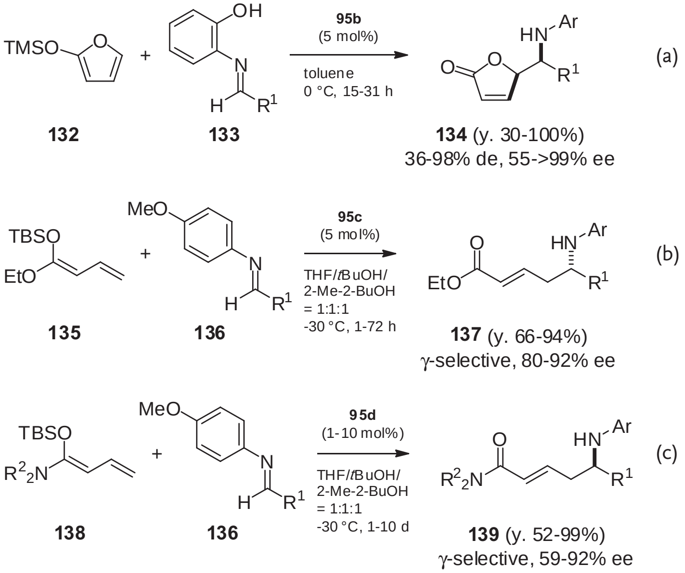
Scheme 28.13 Phosphoric acid-catalyzed intramolecular aldol reactions.

28.3.2
Mannich Reactions with Brønsted Acid and Hydrogen-Bond Catalysis

28.3.2.1 Vinylogous Mukaiyama Mannich Reactions with Brønsted Acid Catalysis

Pioneering research on the chiral phosphoric acid-catalyzed Mukaiyama Mannich reaction was reported in 2004 [68]. The vinylogous Mukaiyama Mannich reactions between silyl enol ethers and α,β-unsaturated carbonyl compounds as the nucleophile were described more recently. Vinylogous Mannich reactions of 2-trimethylsiloxyfuran (**132**) with imines (**133**) catalyzed by the chiral phosphoric acid **95b** with iodine at the 6,6′-positions on the binaphthyl group afford γ-butenolide derivatives (**134**) with high diastereo- and enantioselectivities (Scheme 28.14a). Calculations indicate that an electronic effect of the iodine substituents, rather than a steric effect, plays a role in selectivity [69]. Highly γ-regioselective vinylogous Mukaiyama Mannich reactions of the imines (**136**) using silyl enol ethers of ester **135** as nucleophiles carried out in the presence of chiral phosphoric acid **95c** provide α,β-unsaturated δ-amino carboxylic esters **137** with the

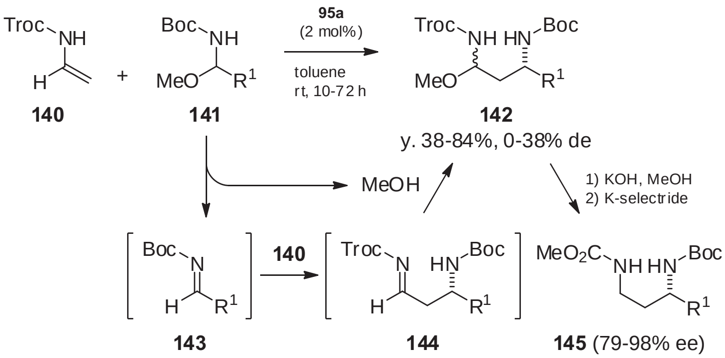
(S)-configuration (R^1 = aryl) in one step (Scheme 28.14b). In addition, imine **136** (R^1 = 4-EtC_6H_4-), formed *in situ* in a direct three-component coupling, also reacts with **135** in 93% yield with 92% ee [70]. Silyl enol ethers of amide **138** undergo vinylogous Mukaiyama Mannich reactions with imines (**136**) catalyzed by 3,3′-bis(triphenylsilyl)-substituted phosphoric acid **95d**. δ-Amino-α,β-unsaturated amides (**139**) with the (R)-configuration (R^1 = aryl) are obtained in good yields with complete γ-regioselectivity (Scheme 28.14-3). When the (R)-BINOL enantiomer is used as the catalyst backbone, phosphoric acid **95c** gives (S)-**139** with 75% ee, but phosphoric acid **95d** bearing an extremely bulky group affords the opposite isomer (R)-**139** with 92% ee [71].



Scheme 28.14 Vinylogous Mukaiyama–Mannich reactions.

28.3.2.2 Mannich-Type Reactions of Enecarbamates with Brønsted Acid Catalysis

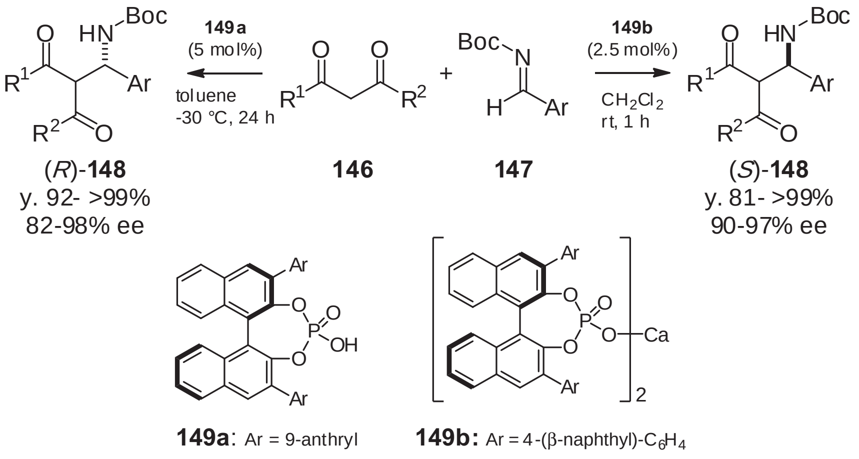
Synthetically important chiral 1-monosubstituted 1,3-diamines (**145**) are synthesized in Mannich-type reactions of enecarbamates (**140**) with aromatic and aliphatic hemiaminal ethers (**141**) in the presence of phosphoric acid **95a**. This process involves the highly reactive Mannich-type product (**144**), which is entrapped by a methanol molecule generated during the formation of the imine (**143**) derived from the hemiaminal ether (**141**) (Scheme 28.15) [72]. Similarly, diastereo- and enantio-enriched *anti*-1,2-disubstituted 1,3-diamines are prepared by the Mannich-type reaction of aldehydes, anilines, and enecarbamates in the presence of chiral phosphoric acid [73].



Scheme 28.15 Mannich-type reactions of enecarbamates.

28.3.2.3 Mannich Reactions Catalyzed by Chiral Calcium Phosphate

The actual catalyst in phosphoric acid-catalyzed Mannich-type reaction of imines with 1,3-dicarbonyl compounds is certainly phosphoric acid itself [74], but metal contaminants, such as alkali or alkaline-earth metals, have interesting effects on the reactivity and stereoselectivity. HCl-washed, metal-free chiral phosphoric acid **149a** and chiral calcium phosphate **149b** are able to catalyze the Mannich-type reactions. The absolute stereoselectivity of the phosphoric acid catalysis is opposite that of the calcium phosphate catalysis (Scheme 28.16) [75].



Scheme 28.16 Chiral phosphoric acid and chiral calcium phosphate.

28.4
Brønsted Base Catalysis Including Bifunctional Catalysis

Organic Brønsted bases have been used to catalyze synthetically valuable carbon–carbon bond forming reactions of carbonyl and related compounds for decades.

With the development of organocatalysis, chiral Brønsted base catalysis has generated significant interest [76]. Nitrogen-containing compounds such as tertiary amines, guanidines [77], amidines, and imidazoles are predominantly used as a chiral Brønsted base catalysts; in particular, the cinchona family is effective due to their extensive versatility, stereochemical diversity, and commercial availability. Bifunctional catalysts such as tertiary amine-thiourea, cinchona-thiourea, and guanidine-thiourea are important in organocatalysis [78]; they are included in this section because reactive intermediates in bifunctional catalysis are often onium enolates or enolate-like species, similar to Brønsted base catalysts.

28.4.1
Aldol Reactions in Brønsted Base Catalysis Including Bifunctional Catalysis

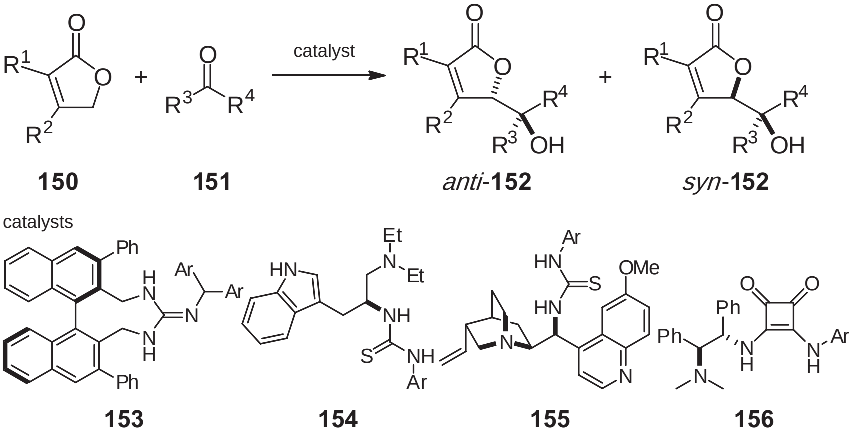
28.4.1.1 Vinylogous Aldol Reactions in Brønsted Base Catalysis

Recently, direct vinylogous aldol reactions of furanones **150** with aldehydes or ketones have been investigated intensively. These reactions are simple alternatives to the vinylogous Mukaiyama aldol reaction of silyloxy furans discussed in Section 28.3.1.1 (Vinylogous Mukaiyama Aldol Reactions in Brønsted Acid Catalysis). Highly enantioselective direct vinylogous aldol reactions of dihalogenated furanones (**150**, $R^1 = R^2 = Cl$) with aldehydes (**151**, $R^3 = H$) are catalyzed by the axially chiral guanidine **153**. The substituent attached to the guanidine moiety significantly impacts the diastereo- and enantioselectivity as well as the catalytic activity. A bis(3,4,5-trimethoxyphenyl)methyl group shows the best results (Table 28.7, entries 1 and 2) [79]. γ-Substituted butenolides containing a tertiary alcohol moiety are provided by the highly *syn*-selective vinylogous aldol reactions between furanones (**150**) and ketoesters (**151**, $R^3 = Ph$, $R^4 = CO_2Bu^t$) catalyzed by the bifunctional catalyst **154** containing tertiary amine, thiourea, and tryptophan moieties (entry 3) [80]. The *anti*-selective vinylogous aldol reactions of the unactivated furanones (**150**, $R^1 = R^2 = H$) with aldehydes (**151**) are achieved by use of cinchona-thiourea bifunctional catalyst **155** under mild conditions (entry 4) [81]. Similarly, bifunctional tertiary amine-squaramide **156** enantioselectively catalyzes the vinylogous aldol reaction, but prolonged reaction times are necessary (entry 5) [82].

28.4.1.2 Nitroaldol (Henry) Reactions with Brønsted Base Catalysis

The reactions of a reactive nitronate species generated from a nitroalkane with an aldehyde or ketone are generally called nitroaldol or Henry reactions [3d]. *Anti*-nitroaldol product **158** is obtained with moderate enantioselectivity in the nitroaldol reaction catalyzed by the axially chiral guanidine base **159** (Table 28.8, entry 1) [83]. Recently, phosphonium salts such as the Wittig reagent, which are readily accessible and important intermediates, have emerged as Lewis acid, Brønsted base, and phase-transfer catalysts in asymmetric organocatalytic reactions [84]. Extremely high diastereo- and enantioselective nitroaldol reactions have been demonstrated with the newly designed chiral tetraaminophosphonium salt (*M*,*S*)-**160**, which is easily prepared in a single step from L-valine-derived diamine. Nitroalkanes (**157**) are deprotonated by triamino(imino)phosphorane **162**, which is

Table 28.7 Direct vinylogous aldol reactions in Brønsted base catalysis.



150 **151** *anti*-**152** *syn*-**152**

153 Ar = 3,4,5-(MeO)$_3$-C$_6$H$_2$ **154** Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$- **155** Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$- **156** Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-

Entry	R^1	R^2	R^3	R^4	Catalyst (conc., mol%)	Conditions	Yield (%)	dr (*anti*:*syn*)	ee (%)[a]	Reference
1	Cl	Cl	H	Ph	**153** (5)	THF, −40 °C, 5 h	90	23:77	99	[79]
2	Br	Br	H	4-MeC$_6$H$_4$	**153** (10)	THF, −40 °C, 12 h	95	14:86	99	[79]
3	Cl	Cl	Ph	CO$_2$Bu^t	**154** (10)	Acetone/THF (1:1), rt, 24 h	88	3:97	93	[80]
4	H	H	H	Ph	**155** (10)	Et$_2$O, 30 °C, 50 h	87	85:15	82[b]	[81]
5	H	H	H	2-Naphthyl	**156** (20)	CH$_2$Cl$_2$, rt, 10 d	73	86:14	95[b]	[82]

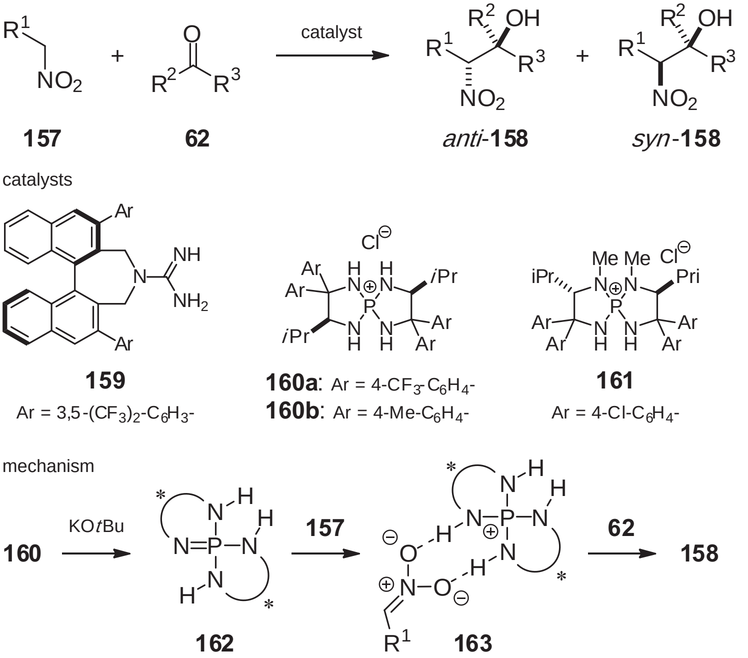
a) The ee is indicated for the major product.
b) Enantiomer ([5*R*,1′*S*]-*ent-anti*-**152**) was obtained.

generated *in situ* from the tetraaminophosphonium salts (**160**) with KOBu^t, and forms a chiral ion pair between nitronate species and protonated phosphorane **162** through two hydrogen bonds. This chiral environment induces *anti*-selective asymmetric direct nitroaldol reactions of nitroalkanes with the aromatic and aliphatic aldehyde electrophiles (entries 2 and 3) [85a]. In addition, chiral *anti*-β-nitro propargylic alcohols (**158**) are synthesized by the direct nitroaldol reaction of ynals catalyzed by **160b** (entries 4 and 5) [85b]. Furthermore, chiral P-spiro tetraaminophosphonium chloride (*P*,*S*)-**161** catalyzes highly *syn*- and enantioselective nitroaldol reactions of pyruvates (entries 6 and 7) [85c].

28.4.1.3 Brønsted Base Catalyzed Aldol Reactions of Isatins

Aldol reactions of unactivated ketones (**164**) with isatins (**165**) are catalyzed by the quinidine-thiourea bifunctional catalyst **166** through an ammonium enolate

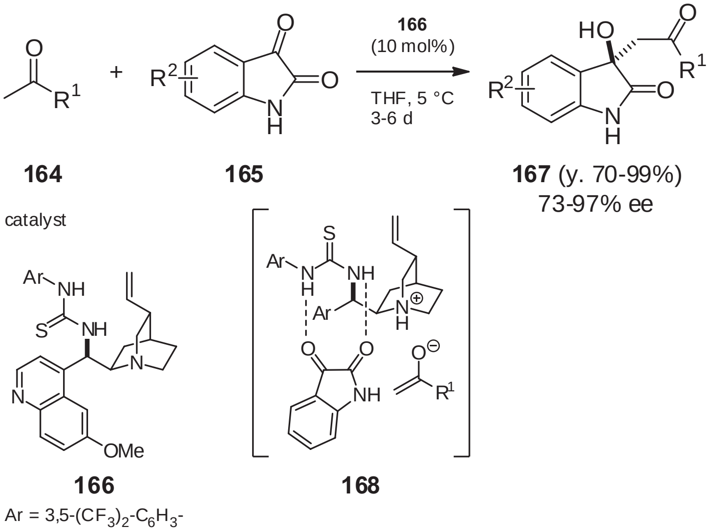
Table 28.8 Brønsted base catalyzed nitroaldol (Henry) reactions.



Entry	R¹	R²	R³	Catalyst (mol%)	Conditions	Yield (%)	dr (*anti*:*syn*)	ee (%)[a]	Reference
1	Me	H	4-MeC$_6$H$_4$	**159** (10)	–80 °C, 72 h	56	76:24	81	[83]
2	Me	H	Ph	**160a** (5)	KO*t*Bu, THF, –78 °C, 8 h	93	>95:5	97	[85a]
3	Et	H	Ph	**160a** (5)	KO*t*Bu, THF, –78 °C, 8 h	78	93:7	96	[85a]
4	Me	H	4-MeOC$_6$H$_4$-CH≡C-	**160b** (5)	KO*t*Bu, THF/DMF, –78 °C, 40 min	>99	>95:5	99	[85b]
5	Et	H	PhCH≡C-	**160b** (5)	KO*t*Bu, THF/DMF, –78 °C, 40 min	92	91:9	93	[85b]
6	Me	Me	CO$_2$Et	**161** (5)	KO*t*Bu, THF, –78 °C, 20 h	76	9:91	86	[85c]
7	Me	Et	CO$_2$Et	**161** (5)	KO*t*Bu, THF, –78 °C, 24 h	55	10:90	92	[85c]

a) The ee is indicated for the major product.

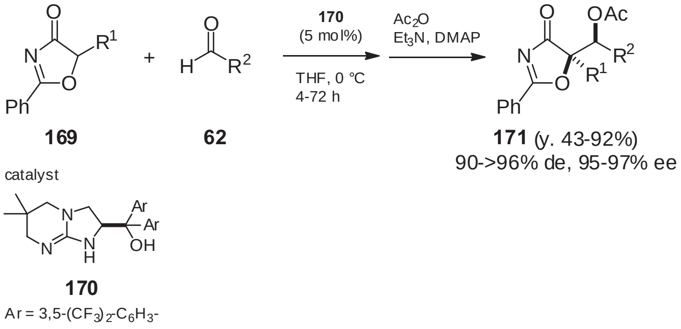
mechanism. The enolate of the ketone **164** closely associates with the catalyst **166** via ionic interactions; in addition, the two carbonyl groups of the isatin **165** are activated by two hydrogen bonds with the thiourea moiety of catalyst **166**. The transition state model **168** is shown in Scheme 28.17 [86]. The reaction results in high yields and enantioselectivities. Similarly, nitroaldol reactions of nitroalkanes with isatins are achieved by use of the cinchona-derived base catalyst [87].



Scheme 28.17 Cinchona-thiourea catalyzed aldol reactions of isatins.

28.4.1.4 Brønsted Base Catalyzed Aldol Reaction of 5*H*-Oxazol-4-ones

The chiral bicyclic guanidine **170** acts as a Brønsted base catalyst. The hydroxy group controls diastereo- and enantioselectivities in the direct aldol reaction of 5*H*-oxazol-4-ones (**169**) with aldehydes (**62**). The aldol products (**171**) are easily converted into amides or esters without loss of enantiopurity; thus, this method provides synthetically useful α,β-dihydroxycarboxylates bearing a chiral quaternary stereogenic center at the α-carbon atom (Scheme 28.18) [88].



Scheme 28.18 Guanidine-base-catalyzed aldol reaction of 5*H*-oxazol-4-ones.

28.4.2
Mannich Reactions in Brønsted Base Catalysis Including Bifunctional Catalysis

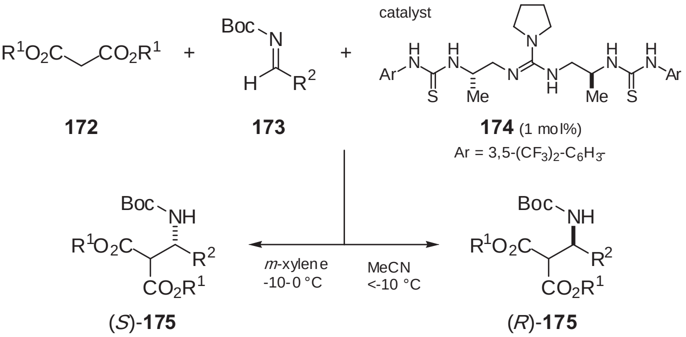
28.4.2.1 Solvent-Dependent Guanidine Base Catalyzed Mannich Reactions

Conformationally flexible guanidine-thiourea catalyst **174** has unique solvent-dependent properties in the catalytic Mannich-type reaction. Based on detailed kinetic analyses, the origin of solvent-dependent stereo-discrimination is controlled by enthalpy–entropy compensation. The stereoselectivities of (*S*)-selective Mannich-type reactions in non-polar solvents such as *m*-xylene are predominantly due to differences in the entropies of activation (Table 28.9, entries 1–3), whereas the stereo-discrimination of (*R*)-selective reactions in polar solvents such as acetonitrile result from differences in the enthalpies of activation (Table 28.9, entries 4–6) [89].

28.4.2.2 Chiral Ammonium Betaine-Catalyzed Mannich Reactions

Quaternary ammonium betaines possessing an anion moiety have emerged as Brønsted base catalysts. The C_2-symmetric axially chiral ammonium betaine **177** deprotonates the α-substituted α-nitrocarboxylates (**176**) to form a structured ion pair that reacts with imines (**173**) to furnish the corresponding *anti*-Mannich

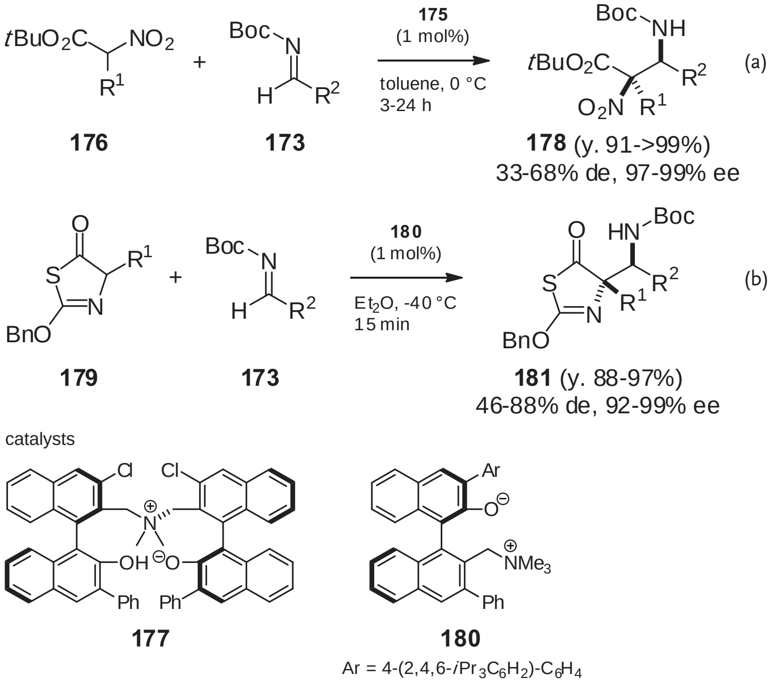
Table 28.9 Solvent-dependent guanidine base-catalyzed Mannich reactions.



Entry	R^1	R^2	Solvent	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	Me	4-MeC$_6$H$_4$	*m*-Xylene	0	1.5	99	+92
2	Me	4-MeOC$_6$H$_4$	*m*-Xylene	0	8	99	+97
3[a]	Bn	Ph	*m*-Xylene	0	2	97	+87
4	Me	4-MeC$_6$H$_4$	MeCN	−40	18	98	−89
5	Me	4-MeOC$_6$H$_4$	MeCN	−40	20	88	−84
6[a]	Bn	Ph	MeCN	−10	2	99	−82

a) Used 5 mol% of **174**.

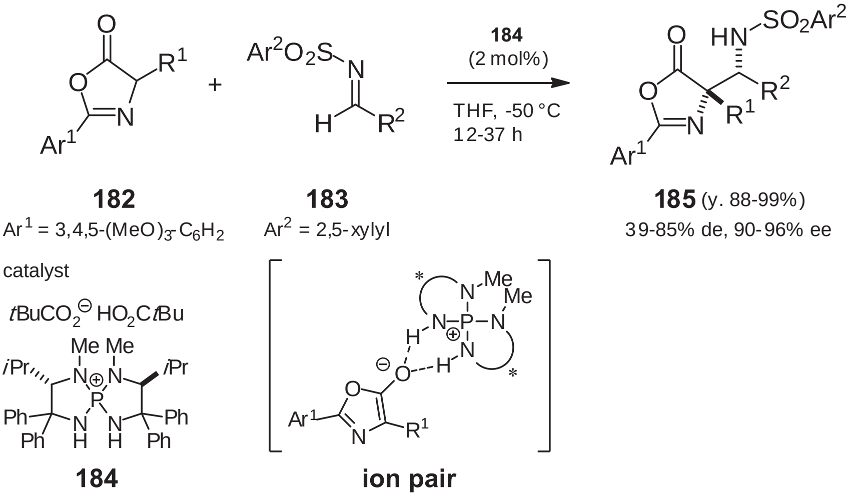
products (**178**) with high enantioselectivities (Scheme 28.19a) [90a]. C_1-Symmetric chiral ammonium betaine also catalyzes enantioselective direct Mannich-type reactions of α-nitrocarboxylates (**176**) [90b]. In addition, the catalyst **180** prepared from readily available (*R*)-1,10-bi-2-naphthol catalyzes the highly stereoselective direct Mannich-type reaction of 2-alkoxythiazol-5(4*H*)-ones (**179**) by forming an intramolecular structured ion pair (Scheme 28.19b) [91].



Scheme 28.19 Chiral ammonium betaine catalyzed Mannich reactions.

28.4.2.3 Quaternary Phosphonium Salt-Catalyzed Mannich Reactions

Newly designed chiral tetraaminophosphonium salt **184** possessing an organic anion cooperatively catalyzes asymmetric Mannich-type reaction of azlactones (**182**) with *N*-sulfonyl imines (**183**) (Scheme 28.20). The basic carboxylate anion deprotonates the active methine proton of the azlactone (**182**) to form the corresponding chiral phosphonium enolate with a defined hydrogen bonding network (ion pair), and then highly stereoselective bond formation proceeds [92].



Scheme 28.20 Tetraaminophosphonium salt-catalyzed Mannich reactions.

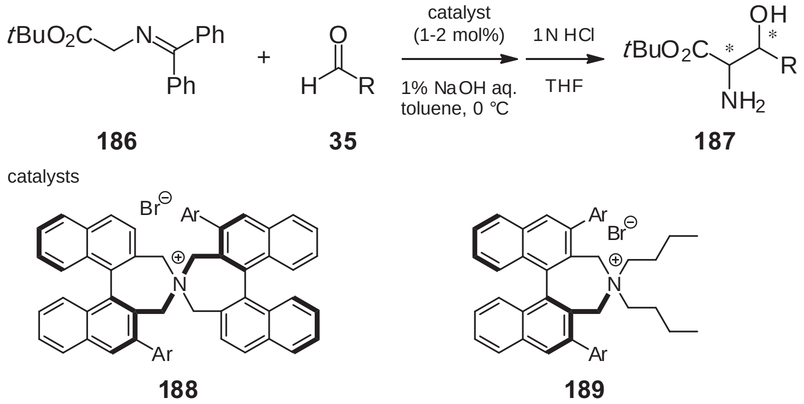
28.5
Phase-Transfer Catalysis

Phase-transfer catalysis is critical not only to industrial manufacturing of high-performance chemical products in low-cost processes but also to academic research on various asymmetric bond formation reactions under mild conditions. The beneficial properties of phase-transfer catalysis such as simple operation, mild conditions, inexpensive reagents and solvents, and large-quantity preparations could open the way to a seamless development of synthetic methods from academia to industry [93].

28.5.1
Aldol Reactions in Phase-Transfer Catalysis

28.5.1.1 Axially Chiral Quaternary Ammonium Salt-Catalyzed Aldol Reactions

The spiro-type phase-transfer catalyst (**188**, Ar = H) possessing a C_2-symmetry axis provides a single type of asymmetric environment; in contrast, a newly designed spiro-type phase-transfer catalyst (**188**, Ar ≠ H) has two different asymmetric environments. The substituents of the binaphthyl subunits affect enantioselectivity, and the 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl group is the best substituent of those evaluated in the *anti*-selective aldol reactions of glycine Schiff base **186** with aldehydes (**35**) (Scheme 28.21) [94]. Similarly, simplified chiral phase-transfer catalyst **189** bearing the 3,5-bis[3,5bis(trifluoromethyl)phenyl] phenyl substituent, which is prepared in a combinatorial approach from the readily available (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid, effectively catalyzes *syn*-selective aldol reactions [95].



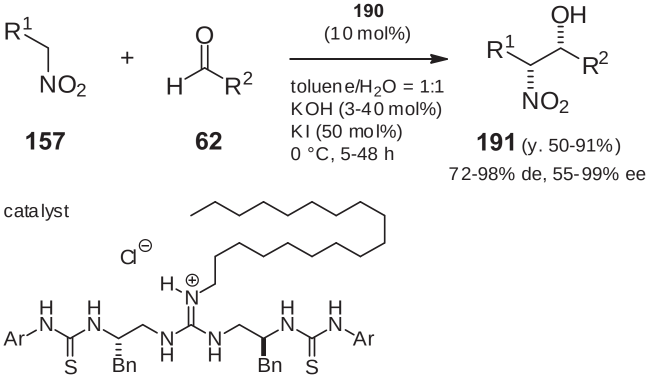
Ar = 3,5-[(3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3
y. 70-90%, 44-64% de (*anti*), 86-90% ee

Ar = 3,5-[(3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3
y. 57-79%, 6-70% de (*syn*), 61-94% ee

Scheme 28.21 Quaternary ammonium salt-catalyzed aldol reactions.

28.5.1.2 Guanidinium-Thiourea-Catalyzed Nitroaldol Reactions

Interfacially active guanidinium-thiourea bifunctional catalyst **190** catalyzes highly enantioselective nitroaldol reactions in the presence of an external base such as KOH in toluene/water biphasic conditions. Although the retro-nitroaldol reactions generally proceed under basic conditions, addition of KI inhibits the retro-process. A cooperative reaction mode between guanidinium and thiourea moieties is supported by experiments using structural variants of **190**. A positive nonlinear effect is observed between the enantiomeric excess of **190** and the product **191**. These results support the hypothesis that self-aggregation of **190** is necessary for catalysis (Scheme 28.22) [96, 97]. Catalyst **190** has been used in the synthesis of chiral tertiary alcohol products obtained in nitroaldol reactions of nitroalkanes and α-ketoesters [98].



190

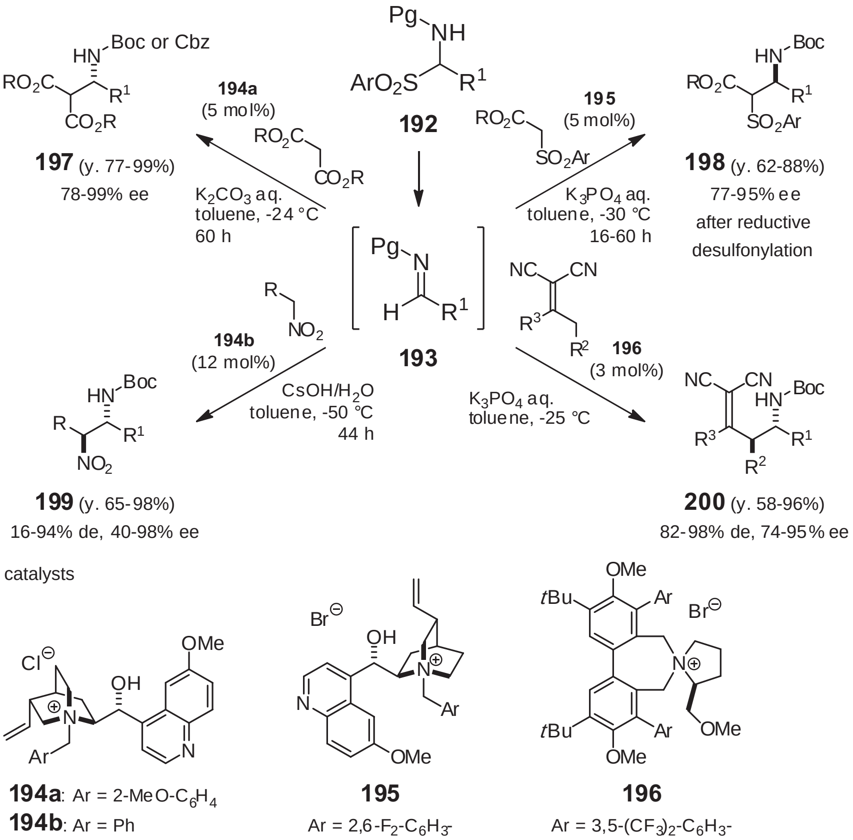
Ar = 3,5-$(CF_3)_2$-C_6H_3-

Scheme 28.22 Guanidinium-thiourea-catalyzed nitroaldol reactions.

28.5.2
Mannich Reactions in Phase-Transfer Catalysis

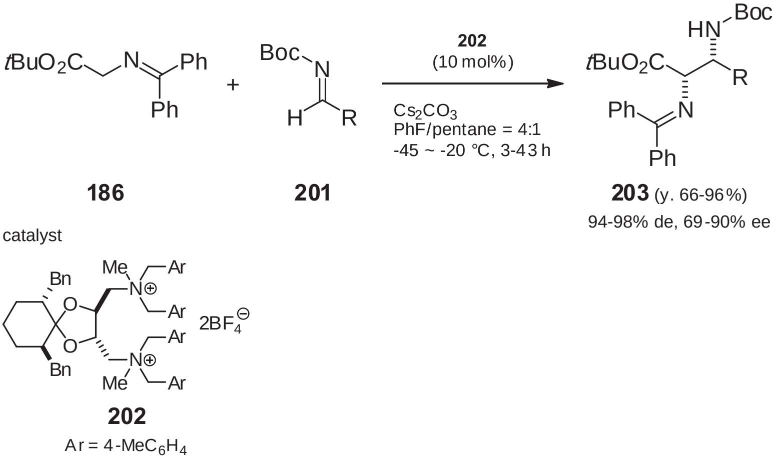
28.5.2.1 Quaternary Ammonium Salt-Catalyzed Mannich Reactions

The synthetic versatility of transformations is significantly dependent on the protecting group on the nitrogen atom of the imine acceptor in Mannich reactions. *tert*-Butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) protecting groups are suitable; however, the imines protected by these groups are relatively unstable. An alternative approach to preparing *N*-Boc or *N*-Cbz protected imine **193**, which is generated *in situ* from protected α-amido sulfones **192** under mild phase-transfer conditions, was developed; examples are Mannich-type reactions using malonates [99] or arylsulfonylacetates [100], aza-nitroaldol reactions [101], and vinylogous Mannich reaction (Scheme 28.23) [102]. Generally, Mannich products are obtained in good to excellent yields and enantioselectivities and can be readily transformed into enantio-enriched key amino compounds in one easy step.



Scheme 28.23 Quaternary ammonium salt-catalyzed Mannich reactions.

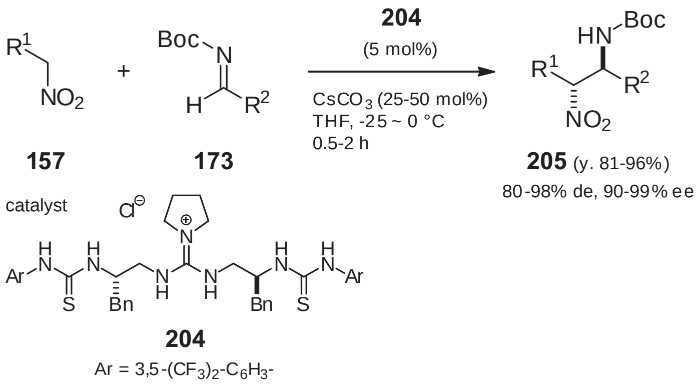
Chiral two-center phase-transfer catalyst **202** possessing 2,6-disubstituted cyclohexane spiroacetal catalyzes the *syn*-selective Mannich-type reaction of glycine Schiff base **186** with *N*-Boc-protected aromatic imines as well as enolizable alkyl imines (**201**) in high yields with moderate to good enantioselectivities (Scheme 28.24) [103].



Scheme 28.24 Two-center quaternary ammonium salt catalyzed Mannich reactions.

28.5.2.2 Guanidinium-Thiourea-Catalyzed Mannich Reactions

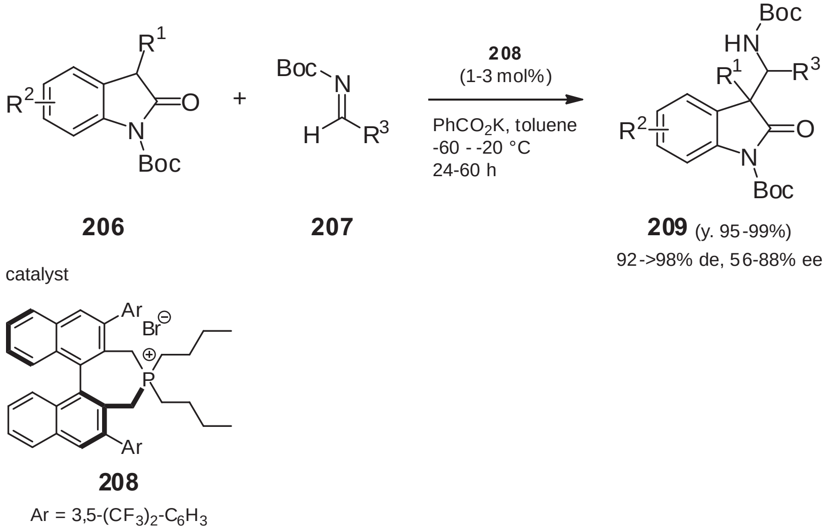
Like the reactions discussed in Section 28.5.1.2, a highly enantioselective aza-nitroaldol reaction of imines (**173**) with nitroalkanes (**157**) is achieved by use of guanidinium-thiourea bifunctional organocatalyst **204** in the presence of external base such as $CsCO_3$ under phase-transfer conditions. Both catalytic activity and enantioselectivity depend upon the substituents on the guanidinium group. The mono-substituted catalyst **190** gives poor results (yield 89%, 9% ee), whereas cyclic amine-substituted catalyst **204** provides excellent enantiomeric excess (Scheme 28.25) [104].



Scheme 28.25 Guanidinium-thiourea-catalyzed Mannich reactions.

28.5.2.3 Quaternary Phosphonium Salt-Catalyzed Mannich Reactions

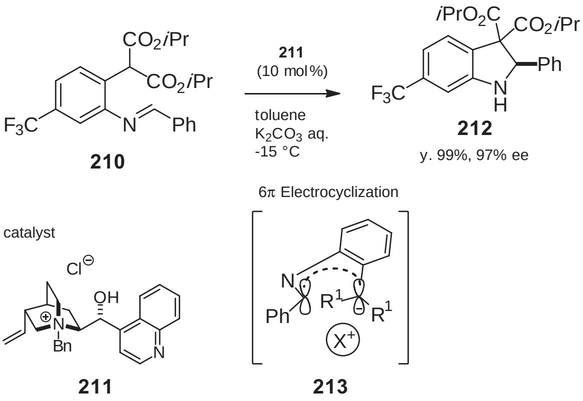
The construction of a quaternary chiral center in 3-aryloxindoles **209** is of interest, since this structure is present in several biologically and pharmaceutically active compounds. Newly designed phosphonium salt **208** catalyzes the Mannich reaction between 3-aryloxindoles (**206**) and activated imines (**207**) in quantitative yields with excellent diastereoselectivity and high enantioselectivity under phase-transfer conditions (Scheme 28.26) [105].



Scheme 28.26 Quaternary phosphonium salt-catalyzed Mannich reactions.

28.5.3
Quaternary Ammonium Salt-Catalyzed 6π Electrocyclization

The intramolecular reaction of *N*-aryl imine **210** under phase-transfer conditions in the presence of cinchonidinium chloride **211** furnishes the chiral indoline **212** in quantitative yield with high enantiomeric excess (Scheme 28.27). An intramolecular Mannich reaction under kinetic control formally constitutes a 5-(*enolexo*)-*endo* trig reaction, which is stereo-electronically demanding as delineated by the Baldwin rules; therefore, this transformation includes a cation-directed 6π electrocyclization as depicted in the reaction model **213** [106].

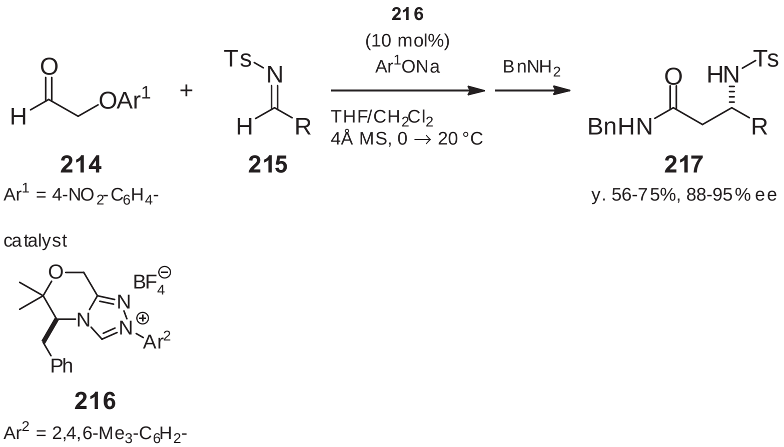


Scheme 28.27 Quaternary ammonium salt-catalyzed 6π electrocyclization.

28.6
N-Heterocyclic Carbene (NHC) Catalysis

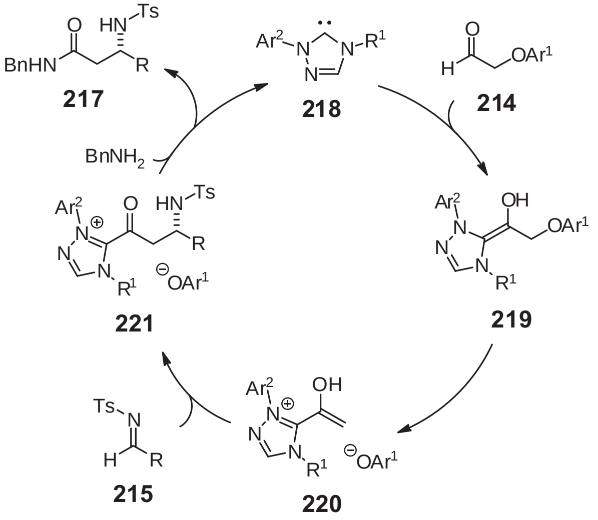
28.6.1
NHC-Catalyzed Mannich-Type Reactions

N-heterocyclic carbene catalysis has become one of the major categories in organocatalysis. Azolium salts are ready deprotonated by weak bases to generate a carbene, which then adds to an aldehyde to form an acyl anion equivalent, generally called the Breslow intermediate. The reactive acyl anion attacks an electrophile to promote the various transformations such as benzoin, Stetter, and redox reactions [107]. Recently, an interesting approach for NHC-catalyzed generation of an enol/enolate intermediate was reported. Enantio-enriched β-amino acid derivatives (**217**) are formed by the reaction between the α-aryloxyaldehyde **214** and *N*-tosyl-imines (**215**) in the presence of phenyalanine-derived azolium salt **216** as a pre-catalyst and aryl phenoxide as a base (Scheme 28.28) [108].



Scheme 28.28 NHC-catalyzed Mannich-type reactions.

The reaction is initiated by the addition of NHC **218** to an α-aryloxyaldehyde **214**. A phenoxide anion is eliminated to generate an enol/enolate (**220**). Asymmetric Mannich-type reactions between **220** and **215** furnish acyl azolium **221**, and the desired product **217** is assembled through an acyl transfer reaction (Scheme 28.29).



Scheme 28.29 Mechanism of NHC-catalyzed Mannich-type reactions.

28.7
Supported Organocatalysis

In general, reaction efficiency, regiochemistry, and stereochemistry can be better predicted in homogeneous catalysis than in heterogeneous catalysis; however, there are limitations to applications of homogeneous systems in the chemical industry. Heterogeneous catalysis is beneficial as the catalysts can be readily separated from the products and reused. Supported organocatalysts are classified as (i) covalently-supported catalysts, (ii) non-covalently supported catalysts, and (iii) biphasic or multiphasic systems (Figure 28.8). Some excellent examples of supported organocatalysts are introduced in this section [109].

28.7.1
Covalently Supported Organocatalysts

28.7.1.1 Magnetically Supported Organocatalysts

Organocatalysts are often covalently anchored to an insoluble support. Polymer and silica gels are commercially available with a wide variety of functional groups [110]. Although nano-scale catalyst recovery is difficult with conventional filtration, very small particles of the supported catalyst would be advantageous because of a large surface-to-volume ratio relative to bulk materials. Recently, the isolation and separation of nano-size catalysts was achieved by using magnetically separable nanoparticles [111]. Magnetic nanoparticle-supported chiral primary amine **222** efficiently and stereoselectively catalyzed aldol reactions under on-water conditions. The catalyst **222** can be recycled magnetically and reused up to 11 times with no significant loss of activity or stereoselectivity (Scheme 28.30) [112].

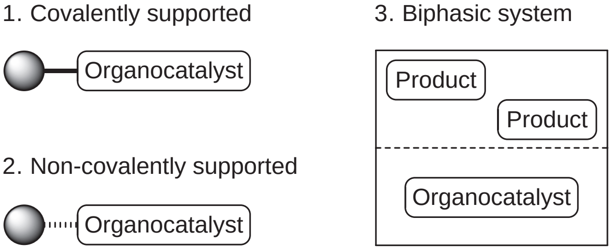
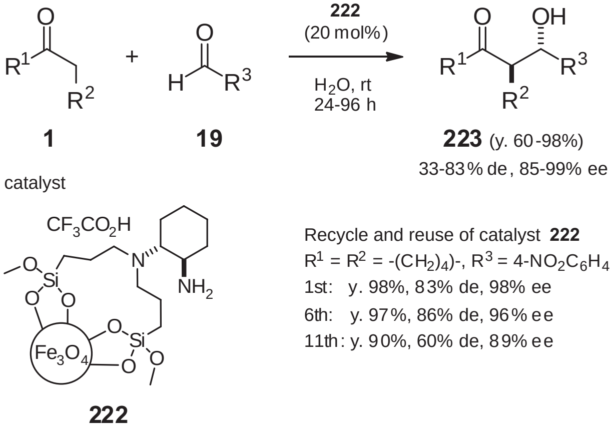


Figure 28.8 Categories of supported organocatalysts.



Recycle and reuse of catalyst **222**
$R^1 = R^2 = \text{-(CH}_2)_4\text{-}$, $R^3 = 4\text{-NO}_2C_6H_4$
1st: y. 98%, 83% de, 98% ee
6th: y. 97%, 86% de, 96% ee
11th: y. 90%, 60% de, 89% ee

Scheme 28.30 Magnetically supported amine-catalyzed aldol reactions.

28.7.2
Non-Covalently Supported Organocatalysts

Organocatalysts are often non-covalently anchored to an insoluble support such as ionic liquid modified-silica, polyelectrolytes, montmorillonite, or β-cyclodextrin. Although bond strength in non-covalently supported catalyst is weak, the catalyst itself is directly used for immobilization without the need for modification or synthetic steps required for covalent attachment to support [113].

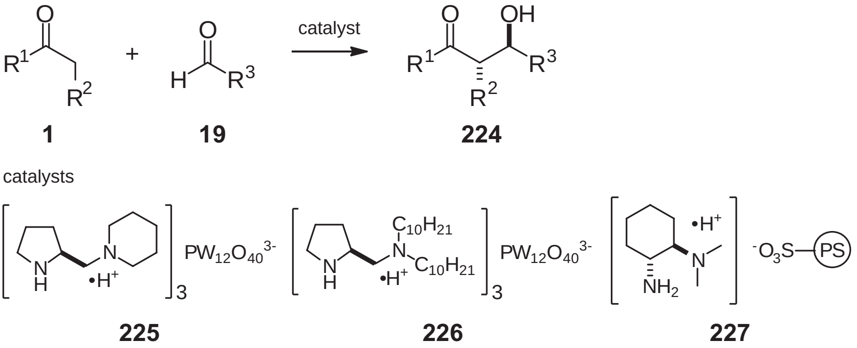
28.7.2.1 Polyoxometalate-Supported Organocatalysts

Polyoxometalates (POMs) are transition metal oxygen clusters with well-defined atomic coordination structures. POMs are used as functional nano-colloidal materials and also as supports for catalysts via ion-pair interactions due to their acidic properties. Combinations of chiral diamines and POM **225** effectively catalyze enamine-based aldol reactions. Less than 1 mol% of chiral amine loading is sufficient to catalyze the reaction (Table 28.10, entries 1 and 2) [114]. Highly diastereo- and enantioselective cross-aldol reactions of aldehydes are accomplished using chiral diamine-POM **226** under emulsion conditions (entries 3 and 4) [115]. Sulfonated polystyrene or fluoropolymer Nafion® NR50 are also good supports for the immobilization of primary–tertiary diamines. The catalyst **227** can be recovered by filtration and reused for at least four cycles with no loss of stereoselectivity (entries 5 and 6) [116].

28.7.2.2 Clay-Supported Organocatalysts

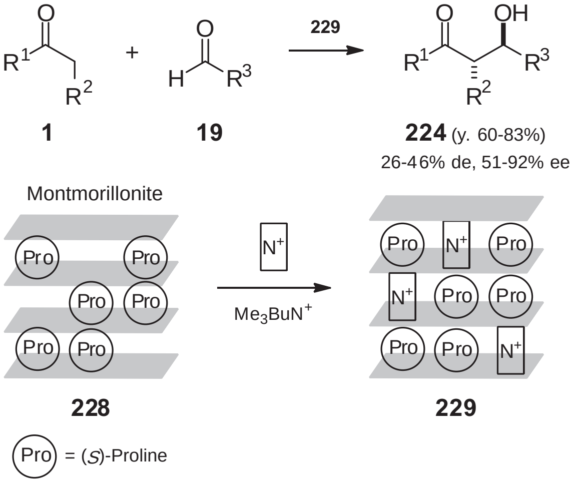
Clays are abundant and available substances that promote various chemical reactions. The characteristic layered structure of clays attracted the attention of synthetic chemists who have used it as a support material [117]. For example, chiral organic–inorganic hybrid materials (**229**) based on (*S*)-proline-exchanged clay such as montmorillonite are used for heterogeneous aldol reactions (Scheme 28.31). Co-inclusion of ammonium cations within the layers enhances yields and

Table 28.10 Polyoxometalate-supported diamine-catalyzed aldol reactions.



Entry	R^1	R^2	R^3	Catalyst (conc., mol%)	Conditions	Yield (%)	dr (*anti*:*syn*)	ee (%)[a]	Reference
1	$-(CH_2)_4-$		$4-NO_2C_6H_4$	**225** (0.33)	Rt, 16 h	99	87:13	99	[114]
2	Me	Me	$4-NO_2C_6H_4$	**225** (0.33)	Rt, 19 h	59	90:10	98	[114]
3	H	Me	$4-NO_2C_6H_4$	**226** (2.5)	H_2O, 0 °C, 24 h	92	>95:<5	99	[115]
4	H	Me	Ph	**226** (2.5)	H_2O, 0 °C, 80 h	80	>95:<5	99	[115]
5	$-(CH_2)_4-$		$4-NO_2C_6H_4$	**227** (10)	CH_2Cl_2, rt, 16 h	97	91:9	97[b]	[116a]
6[c]	$-(CH_2)_4-$		$4-NO_2C_6H_4$	**227** (10)	CH_2Cl_2, rt, 34 h	95	92:8	96[b]	[116a]

a) Enantiomeric excess for the *anti* diastereomer.
b) Enantiomer of **224** was obtained as a major product.
c) After four cycles.



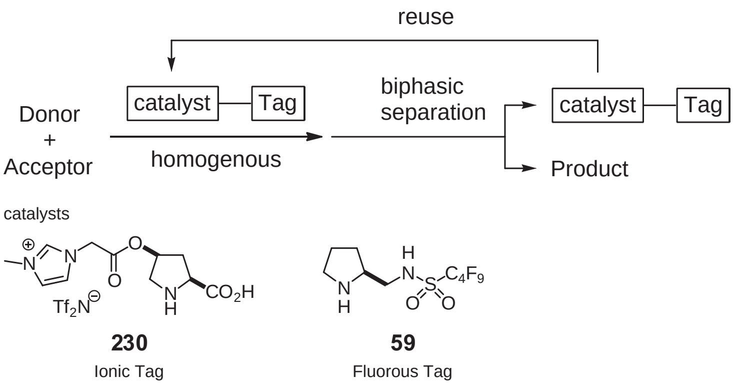
Scheme 28.31 Clay-supported (*S*)-proline-catalyzed aldol reactions.

stereoselectivities. Upon recycling catalyst **229** showed no decrease in enantioselectivity or conversion after ten cycles (Scheme 28.31) [118].

28.7.3
Supported Organocatalysts in Multiphasic Systems

28.7.3.1 **Tagged Organocatalysts**

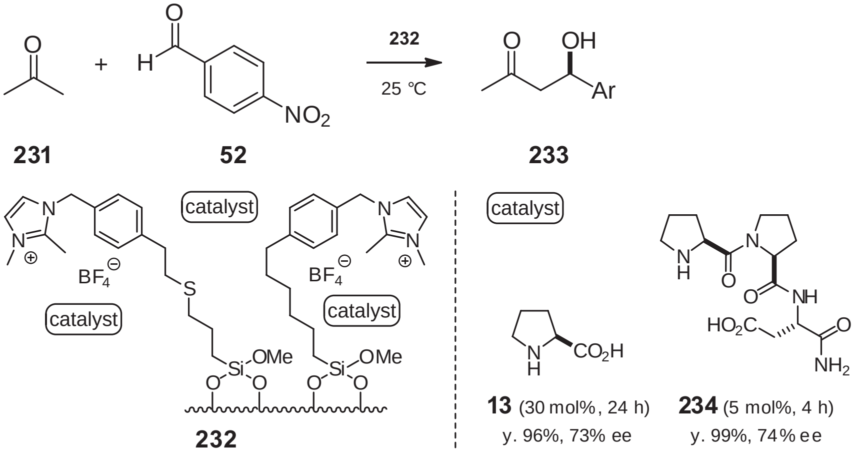
Despite the advantage of easy separation in solid-phase synthesis, the use of insoluble solid-supported catalysts sometimes requires long reaction times and gives low chemical yields and low stereoselectivity. Liquid-phase syntheses using soluble linear polymers as catalyst supports have been developed to improve the chemical reactivities [119]. Ionic or fluorous tags have been employed in organocatalytic transformations in recent years [120–122]. Ionic-liquid supported catalysts provide results similar to those obtained in homogeneous systems. Polar ionic-liquid-supported catalysts are precipitated through biphasic separation by adding a less polar solvent into the reaction mixture, and the recovered catalyst can be reused (Scheme 28.32). For example, imidazolium-tagged *cis*-4-hydroxy-(*S*)-proline **230** catalyzes aldol reactions at a remarkably low catalyst loading (0.1 mol%) [123]. Fluorous (*S*)-pyrrolidine sulfonamide **59** is also a very effective catalyst of the aldol reaction in water. Fluorous separation allows catalyst recovery and reuse for seven cycles without a significant loss of catalytic activity or stereoselectivity [35d].



Scheme 28.32 Tagged organocatalysts.

28.7.3.2 **Supported Ionic Liquid Phase Catalysis**

Highly polar organocatalysts such as amino acids and peptides are almost insoluble in conventional organic solvents, but they are soluble in ionic liquids. Because of these physical properties, asymmetric syntheses in ionic liquids under biphasic condition have been reported [124]. Recently, combinations of solid catalysts and ionic liquids have been studied intensively. The supported ionic liquid phase catalyst is a new generation of the supported liquid-phase catalyst [125]. The supported ionic liquid phase catalyst **232** is readily prepared by adsorption of (*S*)-proline **13** or the peptide **234** onto the surface of silica gels covalently functionalized with an ionic monolayer. These supported catalysts catalyze the aldol reaction between acetone (**231**) and the aldehyde **52** to give the desired product **233** in high yield. The supported catalyst **232** is easily recovered by filtration and can be used several times without loss of either conversion or selectivity (Scheme 28.33) [126].



Scheme 28.33 Supported ionic liquid phase catalyst.

28.8
Summary and Conclusions

The past two decades have been an age of exploration and discovery in organocatalysis, and new and powerful synthetic tools have been developed. The catalytic asymmetric assembly of readily available precursor molecules gives rise to complex products with extremely high stereoselectivity under operationally simple and in some cases environmentally friendly experimental conditions. Nevertheless, some limitations still exist, and there are strong demands for the refinement and design of alternative catalysts that are over 100 times more active than currently available reagents and afford more complicated molecules with perfect stereoselectivity. We believe that this rapidly growing field will rise to meet these challenges in the near future.

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29

Additions of Nitroalkyls and Sulfones to C=X

Aitor Landa, Rosa López, Mikel Oiarbide, and Claudio Palomo

29.1

Organocatalytic Addition of Nitroalkanes to C=O (The Henry Reaction)

The Henry reaction is a base-catalyzed C–C bond-forming reaction between nitroalkanes and aldehydes or ketones. It is similar to the aldol addition, and is also referred to as the nitroaldol reaction. Since its discovery in 1895 [1] the Henry reaction has become one of the most useful reactions for the formation of C–C bonds, and most particularly for the synthesis of β-nitroalcohol derivatives [2]. The general features of this reaction are: (i) the potential offered by the nitro and hydroxyl groups on the products for transformation into other compound families such as β-amino alcohols, β-amino acids, or nitroalkenes; (ii) only a catalytic amount of base is required; (iii) up to two contiguous stereogenic centers may be created in a single step concomitantly to the C–C bond formation. Several recent reviews with a focus on the asymmetric Henry reaction and its applications have appeared [3].

Recently, asymmetric reactions catalyzed by metal-free compounds (organocatalysis) have received increased attention due to the potential advantages of these types of systems [4]. This is primarily due to the operational simplicity and the obvious industrial applications. This chapter covers recent developments, from 2007 to date, in the area of the enantioselective organocatalytic Henry reaction with an emphasis on catalytic methods based on Brønsted bases, Brønsted acids, and phase-transfer conditions (PTC) approaches.

While these organocatalysts comprise a considerably broad structural/functional spectrum, a common requirement for them to work efficiently in the Henry reaction appears to be the presence of (i) a basic unit to generate the nucleophilic nitronate species and (ii) some hydrogen bond donor sites capable of interacting with the acceptor carbonyl group.

29.1.1

Organocatalytic Addition of Nitroalkanes to Aldehydes

The first catalytic asymmetric version of the Henry reaction with aldehydes was reported by Shibasaki in 1992 and was based on bifunctional multimetallic

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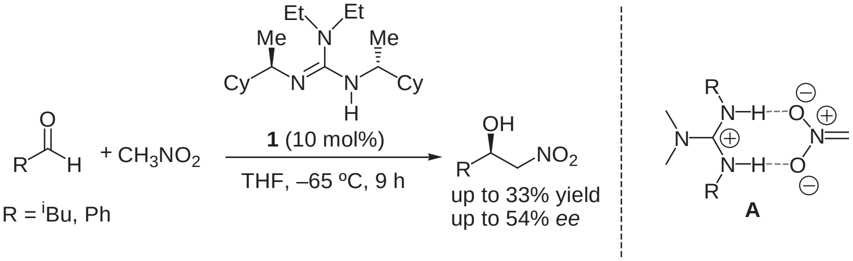
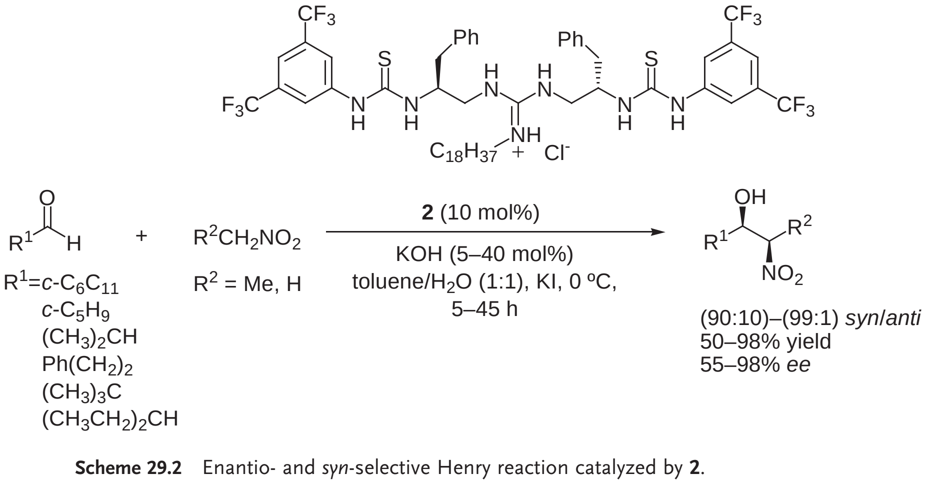
catalysis [5]. The pioneering report on an asymmetric organocatalytic Henry reaction appeared in 1994, when Nájera documented that the reaction of isopentenal and benzaldehyde with nitromethane can be catalyzed by *C*2-symmetric guanidine base **1** to give the corresponding β-nitroalcohol derivatives with moderate yields and enantioselectivities (Scheme 29.1) [6]. The chiral guanidine **1** acts as a chiral Brønsted base that forms, upon deprotonation of nitromethane, complex **A** linked by two hydrogen bonds.



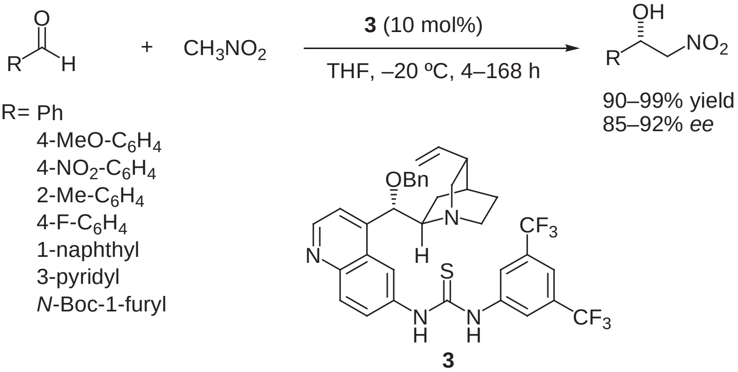
Scheme 29.1 Enantioselective Henry reaction catalyzed by **1** and the proposed mechanistic model (**A**).

Organocatalytic Henry reactions with synthetically useful levels of yields and enantioselectivities came a decade later with the independent work of Nagasawa and Hiemstra. Nagasawa used guanidinium salt/thiourea bifunctional catalyst **2** for the reaction of nitromethane or nitroethane with aliphatic aldehydes (no reaction was observed when aromatic aldehydes were used) [7]. The reaction works under PTC with the assistance of KOH, and to overcome the retro-nitroaldol reaction KI as an additive was required (Scheme 29.2). Two years later, the same group extended this reaction to nitroalkanes other than nitromethane, a process that yields the corresponding *syn*-nitroalcohols preferentially.



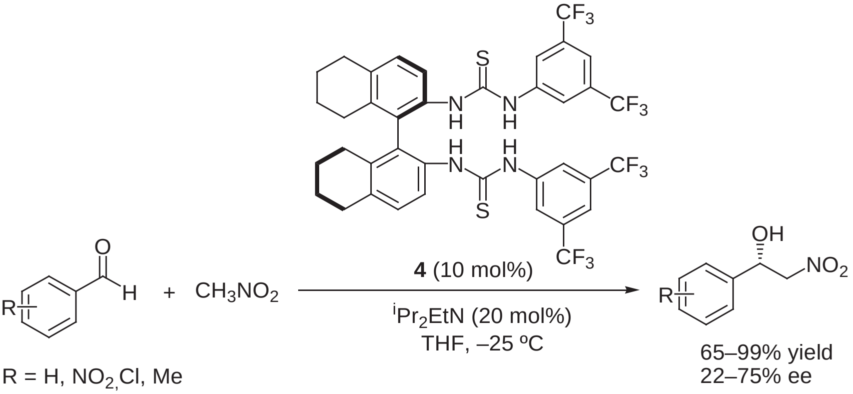
Scheme 29.2 Enantio- and *syn*-selective Henry reaction catalyzed by **2**.

At almost the same time, and based on their earlier studies with cinchona alkaloid organocatalysts bearing both a Brønsted-base and thiourea residues, Hiemstra and coworkers were able to achieve good enantioselectivities and yields in the Henry reaction between aromatic aldehydes and nitromethane [8]. With unactivated aromatic aldehydes (i.e., R = 4-MeO-Ph) longer reaction times were required (Scheme 29.3).



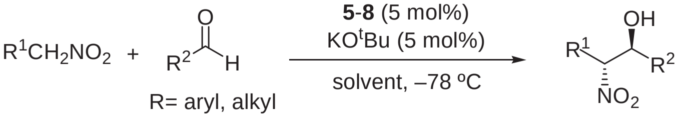
Scheme 29.3 Bifunctional thiourea **3** catalyzed Henry reaction.

After these pioneering studies, some additional developments have appeared, which are summarized below. The enantioselective nitroaldol reaction in the presence of an axially chiral bis(arylthiourea) organocatalyst **4** has been investigated by the Shi group (Scheme 29.4) [9]. The reaction requires 10 mol% of catalyst **4** and the presence of $^{i}Pr_2NEt$ (20 mol%) as co-catalyst and works nicely (65–99% yield) with aromatic aldehydes, although enantioselectivities are at best moderate (22–75% ee). Aromatic aldehydes with electron-donating substituents on the ring showed slightly lower reactivity.



Scheme 29.4 Bis(arylthiourea) **4** catalyzed Henry reaction.

Table 29.1 Substrate scope and reaction conditions for the **5**–**8** catalyzed Henry reaction.

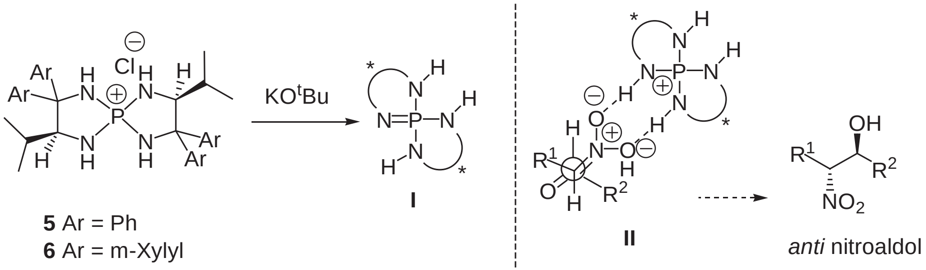


Catalyst	R¹	R²	Solvent	Time (h)	Yield (%)	*Anti*:*syn*	ee (%)	Reference
5	H	Ph	THF	8	86	–	89	[10]
6	H	Ph	THF	8	36	–	45	[10]
7	H	Ph	THF	8	90	–	94	[10]
7	Me	Ph	THF	8	97	>19:1	97	[10]
7	Et	Ph	THF	8	96	13.1	96	[10]
7	Et	4-Cl-Ph	THF	9	95	>19:1	97	[10]
7	Et	4-Me-Ph	THF	24	90	>19:1	97	[10]
7	Et	(*E*)-PhCH=CH	THF	21	74	>19:1	99	[10]
7	Et	$Ph(CH_2)_2$	THF	24	76	4:1	93	[10]
7	Et	$Me(CH_2)_7$	THF	24	77	4:1	93	[10]
7	Me	PhC≡C	THF	0.8	22	>20:1	86	[11]
7	Me	PhC≡C	THF/DMF[a)]	0.8	49	14:1	82	[11]
7	Me	PhC≡C	THF/DMF[a)]	0.8	99	12:1	83	[11]
8	Me	PhC≡C	THF/DMF[a)]	0.8	94	>20:1	98	[11]
8	H	PhC≡C	THF/DMF[a)]	0.8	92	–	88	[11]
8	Et	PhC≡C	THF/DMF[a)]	0.8	92	10:1	93	[11]
8	Me	4-MeO-PhC≡C	THF/DMF[a)]	0.8	99	>20:1	99	[11]
8	Me	$Me(CH_2)_5C≡C$	THF/DMF[a)]	0.8	99	>20:1	98	[11]
8	Me	$Me(CH_2)_5C≡C$	THF/DMF[a)]	0.8	99	>20:1	98	[11]

a) DMF 5–10% (v/v).

The use of chiral *P*-spiro salts **5**–**8** in a nitroaldol reaction was recently reported by the Ooi group (Table 29.1) [10]. The reaction proceeded in the presence of 5 mol% of the chiral tetraaminophosphonium salt and KO^tBu (5 mol%). It was postulated that the nitroalkane would be deprotonated by triaminoiminophosphorane **I**, which would be the actual catalyst generated *in situ* from **5**–**8** and a strong base, forming a chiral phosphonium nitronate complex. An acyclic transition state model **II** predicting the formation of the *anti* adduct was proposed in which the *Si*-face of the nitronate would be set up to approach the *Re*-face of the aldehyde without significant sterical hindrance (Scheme 29.5).

As shown in the Table 29.1, the screening of several chiral tetraaminophosphonium salts, in the test Henry reaction of nitromethane and benzaldehyde, showed that the aromatic substituent (Ar) on the diazaphosphacycle has a significant effect on catalyst efficiency. Thus, while catalyst **5** (Ar = Ph, 86% yield and 89% ee), and especially **6** (Ar = *m*-Xylyl, 36% yield and 45% ee), shown suboptimal performance, catalyst **7** (Ar = $p\text{-}CF_3\text{-}C_6H_4$) provides the corresponding final nitroaldol with



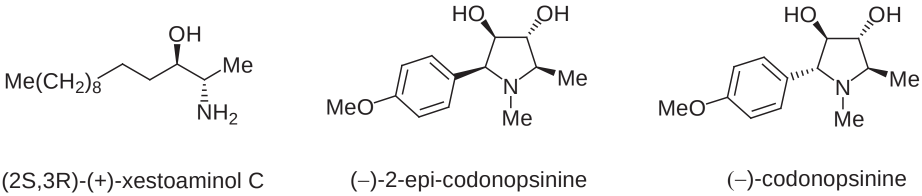
5 Ar = Ph
6 Ar = m-Xylyl
7 Ar = p-CF$_3$-C$_6$H$_4$
8 Ar = p-Me-C$_6$H$_4$

Scheme 29.5 Proposed mechanism for the phosphonium salt mediated asymmetric Henry reaction.

excellent yield and enantioselectivity (90% yield, 94% ee). The reaction proceeded with high (>19 : 1) *anti* : *syn* ratios and excellent (97–99%) enantioselectivities using nitroalkanes other than nitromethane (R^1 = Me, Et), for both electron-rich and -poor benzaldehydes and for α,β-unsaturated aldehydes. In contrast, aliphatic aldehydes led to much lower (4 : 1) *anti* : *syn* ratio.

To make this methodology more useful, the authors extended its scope to ynals as acceptors [11]. Interestingly, higher reactivity is observed and a small amount of a polar solvent that can stabilize the amino phosphonium alkoxide intermediate is essential for good performance (99% yield using 10 mol% DMF). With ynals as aldehydes, slightly better results in terms of selectivity were obtained using catalyst **8** (Ar = *p*-Me-C$_6$H$_4$, *anti* : *syn* >20 : 1, 98% ee) instead of catalyst **7** (Ar = *p*-CF$_3$-C$_6$H$_4$, *anti* : *syn* >12 : 1, 83% ee). In general, the resulting nitroaldol products were formed in good yields, *anti* : *syn* ratios of >10 : 1, and enantioselectivity of up to 99%. Notably, the reaction also proceeds well when aliphatic ynals are used as substrates.

The synthetic utility of the addition of nitroalkanes to ynals is demonstrated by its application in the short synthesis of biologically active compounds, for example, (2*S*,3*R*)-(+)-xestoaminol C, (−)-codonopsinine, and (−)-2-epi-codonopsinine (Figure 29.1).



(2S,3R)-(+)-xestoaminol C
(with catalyst ent-**8**)

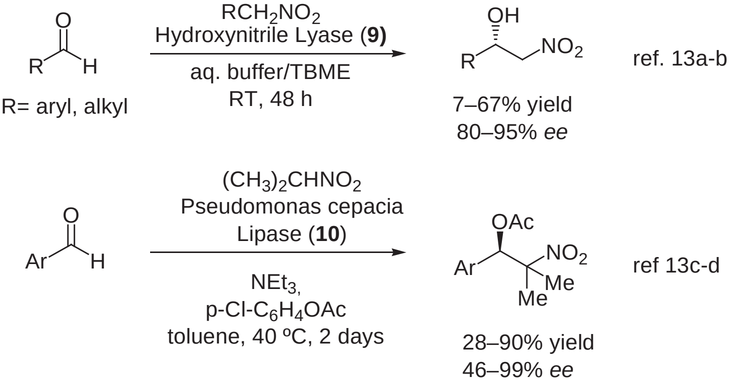
(−)-2-epi-codonopsinine

(−)-codonopsinine

Figure 29.1 Biologically active compounds synthesized employing the Henry reaction as a key step.

Pitchumani and coworkers have found that per-6-amino-β-cyclodextrin (per-6-ABCD) catalyzes efficiently the Henry reaction in aqueous media [12]. Thus, a series of aldehydes react with nitromethane or nitroethane to afford the corresponding β-nitroalcohol derivatives in excellent yields (88–99%) and selectivities (dr > 15 : 1 and 79–99% ee) when using aromatic aldehydes, whereas aliphatic aldehydes afforded variable results (72–88% yield, 52–79% ee).

In addition to the "classic" chemical procedures, the importance of nonchemical methods has increasingly grown in recent years. In particular, enzymatic methods have been utilized for the production of enantioenriched β-nitroalcohol derivatives (Scheme 29.6) [13]. For instance, hydroxynitrile lyase (**9**) was able to catalyze the Henry reaction of nitromethane and nitroethane, affording variable results for both aromatic and aliphatic aldehydes [13a,b]. On the other hand, the one-pot combined nitroaldol reaction and esterification of aromatic aldehydes catalyzed by *Pseudomonas cepacia* lipase **10**, employing 2-nitropropane, produced the corresponding adducts with good yields and enantioselectivities typically higher than 90%; low (28–35%) yields were obtained with aldehydes bearing electron-donating substituents [13c,d].



Scheme 29.6 Enzyme-catalyzed and enzyme-resolved Henry reactions.

Recently, Yashima *et al.* showed that optically active helical polymers bearing cinchona alkaloid derivatives as the pendant group efficiently catalyze the reaction of nitromethane with electron-poor aromatic aldehydes (up to 87% yield, 94% ee) [14]. Interestingly, these polymers exhibited a higher enantioselectivity than the monomeric chiral units on their own, demonstrating the important role of the induced helical chirality of these polymeric catalysts.

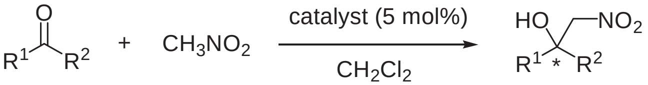
29.1.2
Organocatalytic Addition of Nitroalkanes to Ketones

The enantioselective Henry reaction with ketones is challenging, owing to the attenuated reactivity of the ketone carbonyl group compared to the aldehyde carbonyl moiety and the high tendency of tertiary nitro-aldol adducts to undergo a retro-addition reaction under basic conditions [15]. Stereoselective construction of chiral tertiary alcohols is an important synthetic task because such a functionality is a well-recognized substrate within several fascinating drug candidates. However, its realization always has been a tricky endeavor [16].

To date, few examples of organocatalytic asymmetric addition of nitromethane to ketones have been reported and all of them involve activated ketones, mainly ketoesters and ketoamides.

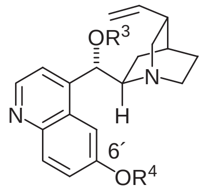
In 2006 Deng and coworkers reported that C6′-OH cinchona alkaloids catalyze the reaction of nitromethane with α-ketoesters to afford the corresponding nitroaldol products with excellent yields and enantioselectivities. The enantioselectivities obtained with C6′-OH cinchona alkaloids were found to be considerably higher than those displayed by C6′-OMe catalyst (Table 29.2, **11** versus **12**) [17].

Table 29.2 Asymmetric Henry reaction of ketones catalyzed by cinchona-derived catalysts.

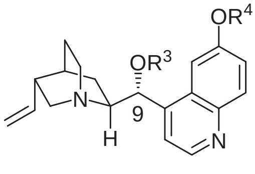


Catalyst	R1	R2	T (°C)	Time (h)	Yield (%)	ee (%)	Reference
11	(E)-$CH_3CH{=}CH$	CO_2Et	–20	14	92	96 (S)	[17]
12	(E)-$CH_3CH{=}CH$	CO_2Et	–20	12	91	17 (R)	[17]
11	Ph	CO_2Et	–20	35	96	95 (S)	[17]
13	Ph	CO_2Et	–20	46	96	93[a] (R)	[17]
11	Me	CO_2Et	–20	12	89	95 (S)	[17]
16	4-Br-Ph	CF_3	0	24	55	0	[19]
14	4-Br-Ph	CF_3	0	24	93	23 (R)	[19]
15	4-Br-Ph	CF_3	–25	48	85	99 (R)	[19]
15	Et	CF_3	–25	48	67	93 (R)	[19]
16	Ph	$P(O)(OEt_2)_2$	RT	28	74	33[b]	[20]
14	Ph	$P(O)(OEt_2)_2$	0	28	71	97[b]	[20]
17	Ph	$P(O)(OEt_2)_2$	RT	14	80	98[b]	[20]
17	Me	$P(O)(OEt_2)_2$	RT	8	79	95[b]	[20]

a) The opposite enantiomer was obtained.
b) The absolute configuration of the major enantiomer was not determined. Reactions carried out in THF.



11 R^3 = Bz , R^4 =H
12 R^3 = H , R^4 =CH_3



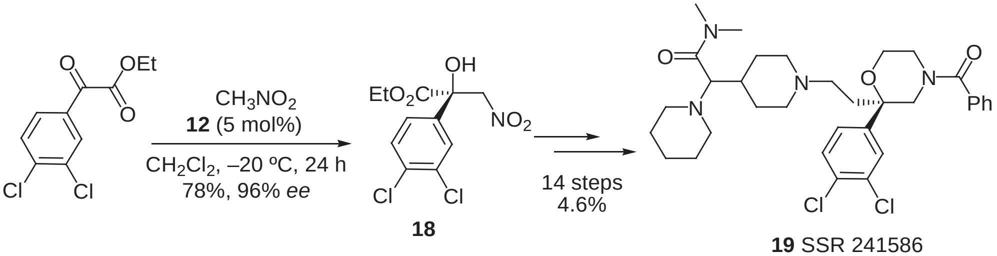
13 R^3 = Bz , R^4 =H
14 R^3 = H, R^4 =H
15 R^3 = 3,5-$(CF_3)_2C_6H_3CO$, R^4 =H
16 R^3 = H, R^4 =CH_3
17 R^3 = Bn, R^4 =H

Notably, the selectivity and yields achieved with pseudoenantiomeric catalysts **11** and **13** are similar albeit with opposite sense of stereoinduction. Starting from both aliphatic and aromatic α-ketoesters and also from α,β-unsaturated ketoesters enantioselectivities in the range of 93–96% ee were obtained.

Fluorinated amino acids and amino alcohols have shown extensive biological activity [18]. In 2008, the Bandini and Umani-Ronchi group developed an efficient Henry reaction between nitromethane and fluoromethyl ketones catalyzed by cinchona alkaloids [19]. They showed that benzoylcupreines bearing electron-withdrawing substituents at the C9 position of the catalyst structure are essential for good results (Table 29.2, **14** versus **15**). Remarkably, comparable levels of asymmetric induction could be obtained with both aromatic and aliphatic ketones.

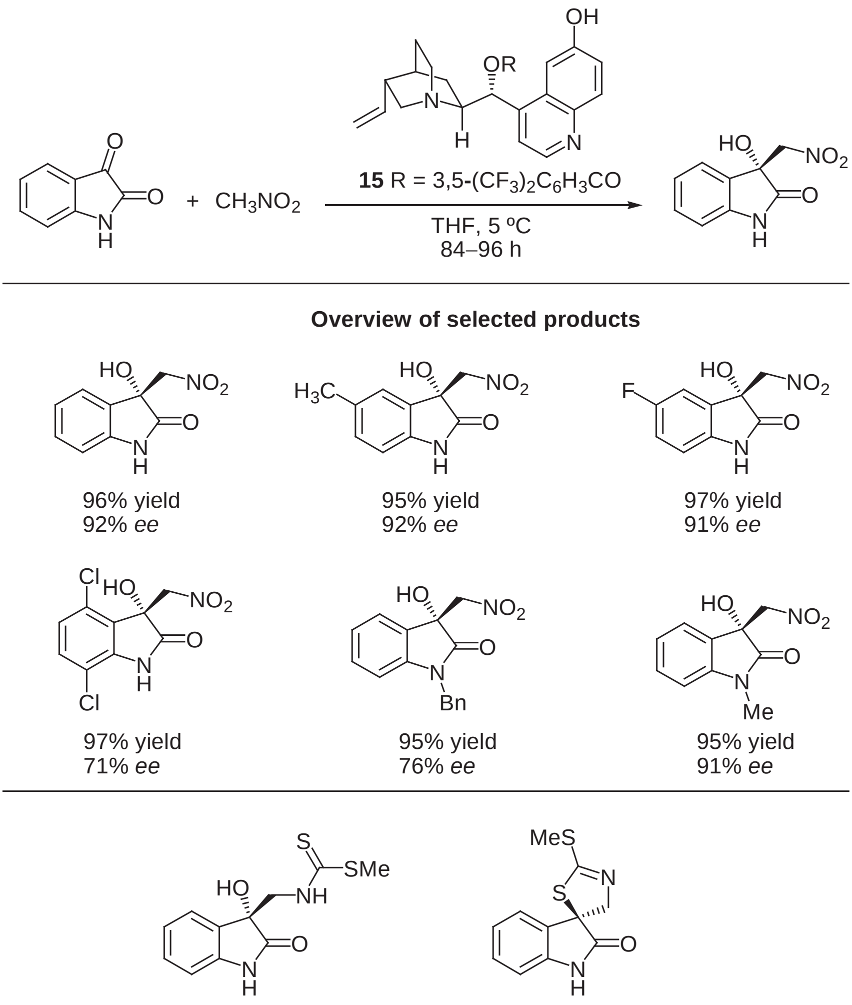
The usefulness of these types of catalysts for the asymmetric nitroaldol reaction of α-ketophosphonates and nitromethane has also been demonstrated [20]. The enantioselectivity achieved with the C6′-OH catalyst was found again to be considerably higher than that displayed by C6′-OMe cinchona alkaloid (**14** 97% ee versus **16** 33% ee). No effects in terms of yield and selectivity were observed on modifying the C9 position of the catalyst (**14** versus **17**). Screening of the solvents revealed that THF is the best one in terms of both reactivity and enantioselectivity. Unfortunately, the absolute configuration of the major enantiomer was not determined.

Deng's strategy was successfully applied by Cossy and coworkers as the key step for the asymmetric synthesis of the antidepressant SSR 241586 chiral core **18** [21]. The Henry adduct **18** was further converted into the SSR 241586 **19** in 14 steps in excellent enantiomeric excess (93% ee) and an overall yield of 4.6% (Scheme 29.7).



Scheme 29.7 Synthesis of SSR 241586.

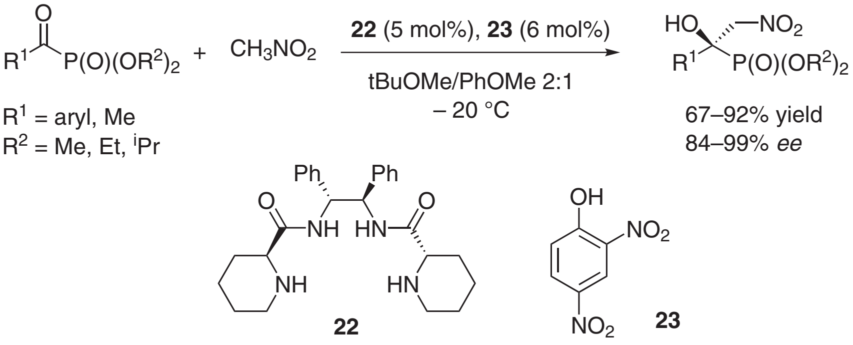
Recently, Wang *et al.* reported the reaction of isatins with nitromethane using C6′-OH cinchona alkaloid catalyst **15** (Scheme 29.8). 3-Substituted 3-hydroxyoxindoles are obtained in excellent yields and enantioselectivities albeit long reaction times are required [22]. For the 4,7-dichloroisatin and *N*-benzyl-isatin, only moderate enantioselectivities were obtained (71% and 76%, respectively). The methodology was applied to the total synthesis of (*R*)-(+)-dioxibrassinin (**20**) and the formal synthesis of (*S*)-(−)-spirobrassinin (**21**).



20 (R)-(+)-dioxibrassinin **21** (S)-(–)-spirobrassinin

Scheme 29.8 Enantioselective Henry reaction between isatins and nitromethane and targeted products (*R*)-(+)-dioxibrassinin (**20**) and (*S*)-(–)-spirobrassinin (**21**).

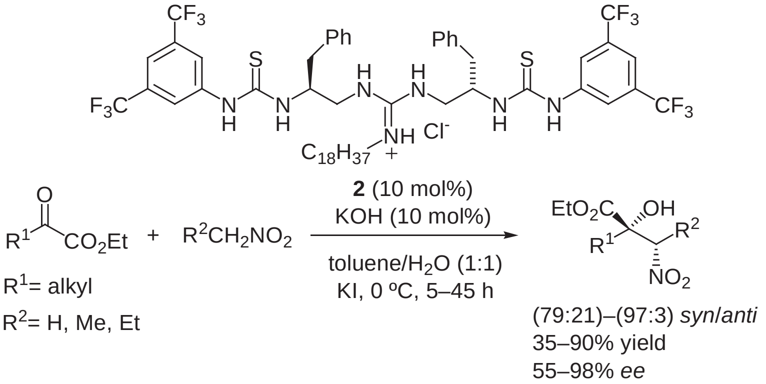
Feng and Hu reported a successful nitroaldol reaction of α-ketophosphonates by using a combination of bis-chiral secondary amide **22** and 2,4-dinitrophenol (**23**) (Scheme 29.9) [23]. In the proposed transition state, one of the piperidine moieties is protonated by the acidic additive, which activates the α-ketophosphonate via hydrogen bonding, and the other piperidine deprotonates nitromethane. With this catalyst system, numerous different nitroaldol compounds may be obtained with high optical purities. A Bu^{t}OMe/PhOMe (2 : 1) solvent mixture seems critical



Scheme 29.9 Enantioselective nitroladol reaction of α-ketophosphonates.

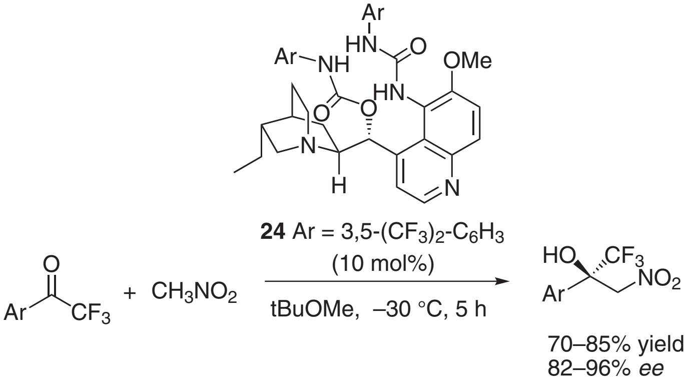
to get high yields and enantioselectivities. The reaction works well for aromatic and aliphatic α-ketophosphonates. The absolute configuration of the final adducts was determined to be (*R*) through X-ray diffraction analysis.

Based on catalytic double activation (guanidinium salt/thiourea moiety skeleton), Nagasawa *et al.* were able to achieve the reaction of nitromethane, nitroethane, and nitropropane with aliphatic α-ketoesters in moderate yields and selectivities (Scheme 29.10) [24]. The reaction works with the assistance of 10 mol% KOH and to overcome the retro-nitroaldol reaction, the presence of 50 mol% KI was required. The resulting Henry reaction adducts are obtained with good *syn/anti* ratios, and enantioselectivities of up to 98%. When aromatic α-ketoesters were subjected to the reaction unsatisfactory results were obtained (e.g., R^1 = Ph, 5% yield and 5% ee).



Scheme 29.10 Chiral salt **2** catalyzed Henry reaction of α-ketoesters.

A new class of chiral bifunctional cinchona-alkaloid catalyst with urea moiety at C5′ has recently been reported by Connon and coworkers, and successfully applied in enantioselective nitroaldol reaction of nitromethane with aromatic trifluoromethyl-ketones (Scheme 29.11) [25]. They propose that the proximity of the urea moiety at the C5′ to the quinuclidine ring is essential for excellent results.



Scheme 29.11 Enantioselective Henry reaction of fluoromethyl ketones catalyzed by **24**.

29.2
Addition of Nitroalkanes to C=NR (The Aza-Henry or Nitro-Mannich Reaction)

The aza-Henry reaction, which is the nucleophilic addition of nitroalkanes to imines, is one of the main existing methods for the synthesis of nitrogen-containing molecules [26]. The resulting β-nitroamines can be either oxidized, producing α-amino carbonyl compounds [27], or reduced to afford 1,2-diamines [28]. By this reaction, both nitrogen functionalities, the amino and the nitro groups, are arranged with simultaneous formation of the new C–C bond while the relative and absolute configurations are all fixed in a single synthetic operation.

Since imines are generally less reactive than aldehydes or ketones, simple imines or Schiff bases are reluctant azomethine substrates for this transformation under smooth reaction conditions. Most useful aza-Henry methodologies involve imines bearing an electron-withdrawing group attached to the nitrogen, such as *N*-acyl, *N*-sulfonyl, or *N*-phosphinoyl groups (Figure 29.2) [29]. These N-activating groups can eventually be removed after the reaction to provide the corresponding NH products. In contrast to the Henry reaction, the aza-Henry reaction employing enolizable aldehyde-derived azomethines is more challenging, owing to the tendency to suffer from α-deprotonation rather than addition. Because of the attenuated reactivity of the azomethine group as compared to the carbonyl, most developments deal with aldimines and a single example involving ketimine substrates has been documented so far. Regarding the nitroalkane partner,

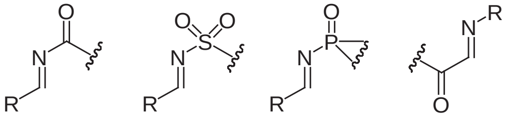


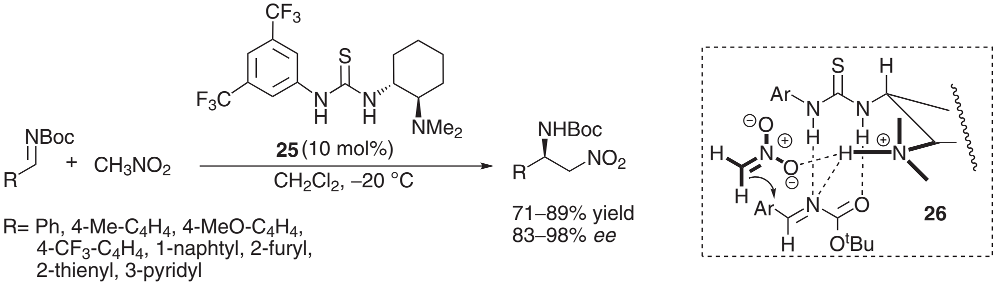
Figure 29.2 Prototypical activated imine substrates.

organocatalytic aza-Henry reactions are most often restricted to nitromethane or nitroethane, both relatively cheap and volatile, and therefore useful in large excess or even as (co)solvent. Longer chain and functionalized nitroalkanes have been scarcely explored.

During recent years, the organocatalytic asymmetric aza-Henry reaction has been investigated more actively than the Henry reaction, resulting in many efficient transformations. For that reason, in the following, the major advances in the field since 2004 are discussed, with the various examples grouped according to the mode of action to which the catalyst is best ascribed [30].

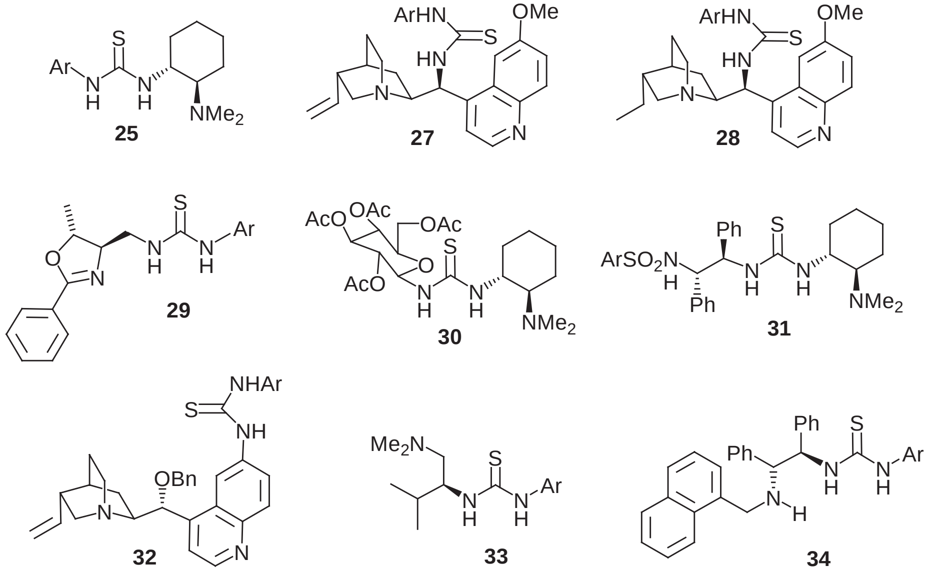
29.2.1
Brønsted Base Catalyzed Aza-Henry Reactions

Two major forms of catalysis action rely on covalent and hydrogen bonding interactions, which are prevalent in amine and Brønsted acid (BA) catalysis, respectively. Ion pairing arises as the third principal interaction between substrates and catalysts, especially when Brønsted base (BB) catalysts are involved. The intrinsic non-directional nature of electrostatic interactions in ion pairing is often offset by incorporating hydrogen-bond donor sites in the catalyst structure (ambifunctional catalyst). As a result, more active catalysts are often obtained. For the purpose of this classification, the latter will also be considered BB catalysts provided that the presence of the BB unit has been demonstrated to be crucial for successful catalytic activity. The first enantioselective organocatalyzed aza-Henry reaction was described employing this type of ambifunctional catalysis. Takemoto reported the organocatalyzed addition of nitromethane to aryl *N*-phosphinoyl imines promoted by the bifunctional thiourea **25**. The reaction carried out at room temperature in the presence of 10 mol% of catalyst, afforded the corresponding adducts in moderate to good yields (57–91%) and moderate enantiomeric excesses (up to 76%) [31]. A subsequent change in the azomethine protection (Boc instead of phosphinoyl group) resulted in a substantial increase in the reaction enantioselectivity. The authors explained the high degree of stereoselectivity by invoking the formation of a ternary complex (**26**) in the transition state (Scheme 29.12) [32].



Scheme 29.12 Enantioselective aza-Henry reaction of *N*-Boc imines catalyzed by **25**, and the proposed transition state model.

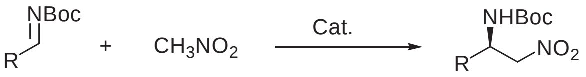
Since Takemoto first demonstrated the effectiveness of the bifunctional thiourea catalyst **25** in the aza-Henry reaction with imines, several chiral BB catalysts (**27–34**) have been reported for this reaction, all maintaining an amine as the basic unit and a thiourea group as the hydrogen bond donor (Figure 29.3). Table 29.3 shows representative data concerning the addition of nitromethane to *N*-Boc



Ar = 3,5-$(CF_3)_2$-C_6H_4

Figure 29.3 Amine-thiourea based bifunctional catalysts for the aza-Henry reaction.

Table 29.3 Bifunctional thiourea-amine catalyzed addition of nitromethane to *N*-Boc imines.

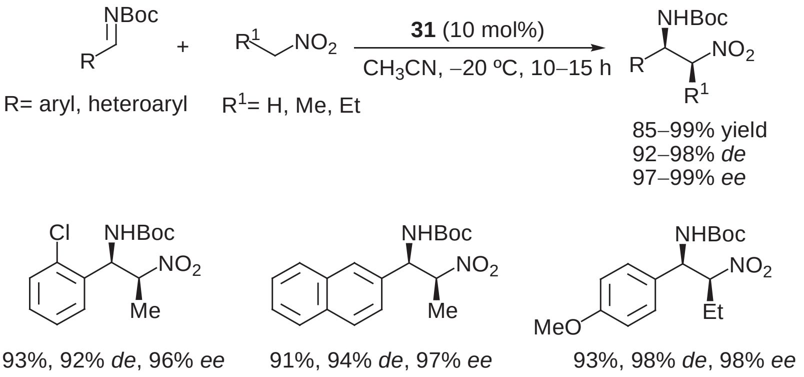


Cat. (mol%)	R	Solvent	*T* (°C)	*t* (h)	Yield (%)	ee (%)	Reference
27 (20)	Aryl, heteroaryl	Toluene	−24	20–72	50–95	80–94[a),b)]	[33]
29 (10)	Aryl	THF	RT	48–63	68–97	73–92	[34]
30 (15)	Aryl, heteroaryl	CH_2Cl_2	−78	39–68	84–95	83–99	[35]

a) Absolute configuration not determined.
b) The reaction with 2-furancarboxyaldehyde derived imine afforded the corresponding adduct in a low 44% ee.

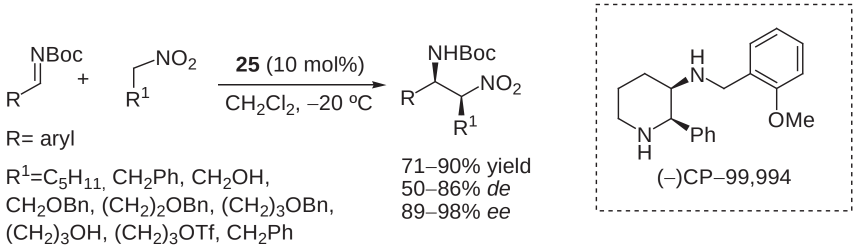
imines using catalysts **27**, **29**, and **30**. The procedures described are restricted to non-enolizable aldehyde-derived azomethines, usually aryl and heteroaryl *N*-Boc-imines. In general, reactions take several days for completion using a catalyst loading of 10–20 mol%. In a related development, the thiourea-based catalyst **28** has been shown to be a highly effective promoter in the addition of nitromethane and nitroethane to *N*-methoxycarbonyl aryl imines to afford β-nitroamines in good yields (60–98%) and high stereoselectivities (90–98% ee, 82–97% de) [36].

The aza-Henry reaction promoted by catalyst **31** deserves special attention. This bifunctional catalyst, which displays an additional hydrogen bond donor, afforded the best results in terms of yield and selectivity for the addition of nitromethane, nitroethane, or 1-nitropropane to various aryl and heteroaryl *N*-Boc imines (Scheme 29.13) [37]. Reactions carried out in acetonitrile at −20 °C, employing 10 mol% catalyst, provided the highest stereoselectivities achieved so far.



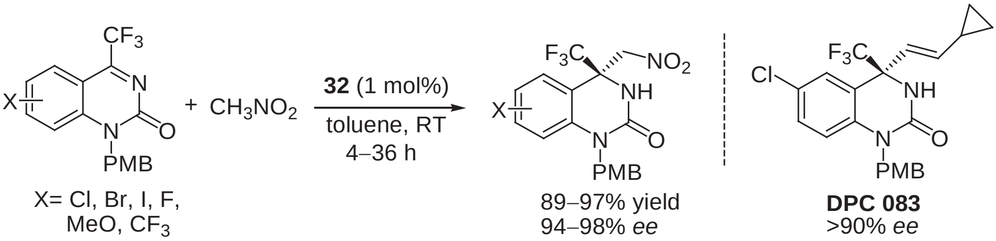
Scheme 29.13 Enantioselective aza-Henry reaction of *N*-Boc imines catalyzed by **31**, and representative examples.

Apart from linear unfunctionalized nitroalkanes, various other prochiral nitroalkanes bearing aryl, alcohol, ether, and ester groups also participate effectively in reactions promoted by **25**, producing *syn*-β-nitroamines in good yields and high enantiomeric excesses [32]. The utility of this methodology was demonstrated by the synthesis of the neurokinin-1 receptor antagonist CP-99,994 (Scheme 29.14).



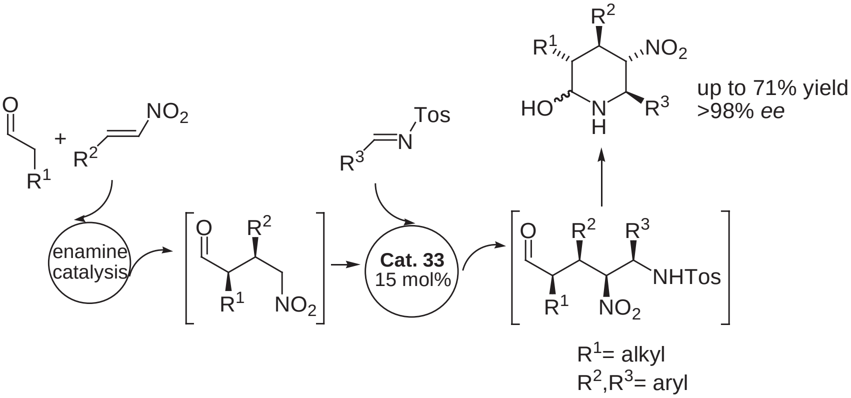
Scheme 29.14 Scope of nitroalkanes in the enantioselective aza-Henry reaction of *N*-Boc imines catalyzed by **25**, and compound CP-99,994 synthesized employing the methodology.

On the other hand, the first highly efficient organocatalyzed aza-Henry reaction of ketimines has been achieved using catalyst **32** under mild reaction conditions and a catalyst loading as low as 1 mol% (Scheme 29.15). The reaction of substituted 2(1*H*)-quinazolinones with nitromethane catalyzed by **32** afforded chiral trifluoromethyl dihydroquinazolinones in high yields and excellent enantiomeric excesses [38]. The application of the methodology to the addition of (2-nitroethyl)cyclopropane allowed, after proper manipulation, the synthesis of highly enantioenriched DPC 083, an anti-HIV drug candidate.



Scheme 29.15 Enantioselective aza-Henry reaction of cyclic trifluoromethyl ketimines, and the anti-HIV drug candidate DPC 083 synthesized by this method. PMB: *p*-methoxybenzyl.

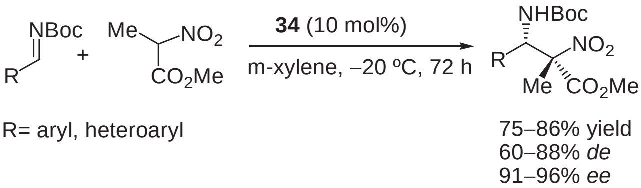
A triple cascade reaction that includes a sequential Michael addition/aza-Henry reaction/cyclization has been described employing BB catalyst **33** (Scheme 29.16) [39]. The three-component cascade reaction catalyzed by two organocatalysts made possible the synthesis of fully substituted highly enantioenriched piperidines.



Scheme 29.16 Proposed cascade sequence for the synthesis of enantioenriched substituted piperidines.

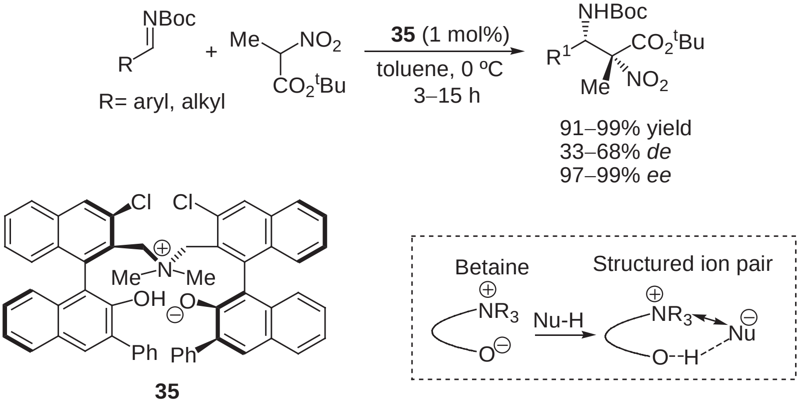
In addition, catalyst **28** has been applied in an organocatalytic asymmetric tandem Michael/aza-Henry reaction between chalcone derivatives and nitromethane to afford the corresponding polysubstituted tetrahydroquinoline derivatives with good yields and high enantio- and diastereoselectivities [40].

An interesting protocol to concurrently produce adjacent quaternary and tertiary stereogenic centers was described employing the bifunctional thiourea-secondary amine **34**, which promotes the addition of methyl 2-nitropropanoate to aryl and heteroaryl *N*-Boc imines. In this particular case, the secondary amine N–H group present in the catalyst seemed to play an additional role other than merely acting as a Brønsted base (Scheme 29.17) [41].



Scheme 29.17 Enantioselective aza-Henry reaction of *N*-Boc imines and methyl-2-nitropropanoate catalyzed by **34**.

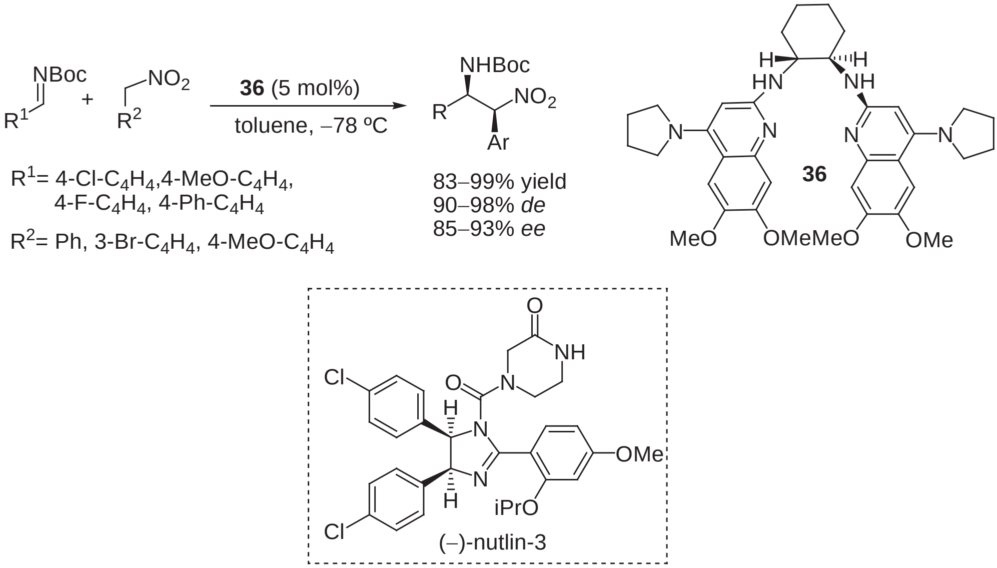
Chiral ammonium betaines are a particular class of bifunctional BB-based catalysts that have been successfully applied in the aza-Henry reaction of *N*-Boc imines and α-substituted α-nitroesters [42]. The catalyst structure displays an intramolecular ion-pairing quaternary ammonium aryl-oxide and the mode of action may involve deprotonation of the pronucleophile by the basic anion to furnish and onium ion as its conjugate acid form. Catalyst loadings as low as 1 mol% produced the corresponding quaternary-tertiary aza-Henry adducts in excellent yields and enantioselectivities, albeit with low to moderate diastereoselectivities (Scheme 29.18). The lowest de's (up to 33%) were obtained with aliphatic *N*-Boc imines (R = CH_2CH_2Ph, *n*-octyl).



Scheme 29.18 Chiral ammonium betaine **35** catalyzed aza-Henry reaction.

As mentioned above, the intrinsic non-directional nature of electrostatic interactions between substrates and monofunctional BB catalysts makes the development of highly selective processes in a predictable manner difficult. As an illustration, the few chiral guanidine organocatalysts that have been described that are capable of promoting the aza-Henry reaction between *N*-Boc aryl imines and nitromethane lead to the corresponding β-nitroamines in generally low enantiomeric excesses (20–70% ee) [43].

A particularly successful case of BB catalyzed aza-Henry reaction is the addition of arylnitromethanes to aryl *N*-Boc imines promoted by chiral bis(amidines) [44]. Reactions carried out in toluene at −78 °C employing 5 mol% of catalyst **36** afford the corresponding aza-Henry adducts in good yields and enantioselectivities and high diastereoselectivities. The methodology has been applied to the synthesis of (−)-nutlin-3, a potent p53/MDM2 inhibitor (Scheme 29.19).



Scheme 29.19 Enantioselective aza-Henry reaction of *N*-Boc imines catalyzed by **36** and its application in the synthesis of (−)-nutlin-3.

29.2.2
Hydrogen Bond Catalyzed Aza-Henry Reactions

Catalysis carried out by activation through hydrogen bonds should be considered as a continuum of bonding interactions, from weak to strong, highly dependent on reaction conditions. Since the strength of a hydrogen bond donor can be correlated to its pK_a, Brønsted acid catalyzed reactions could be considered a particular case of hydrogen bond activation.

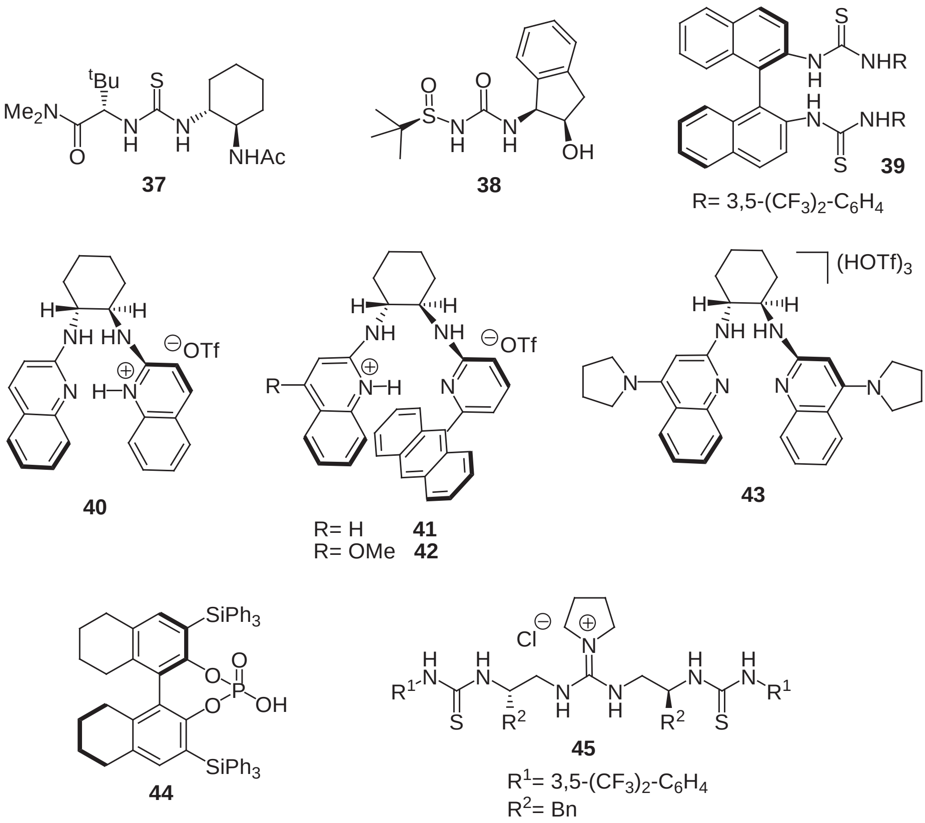
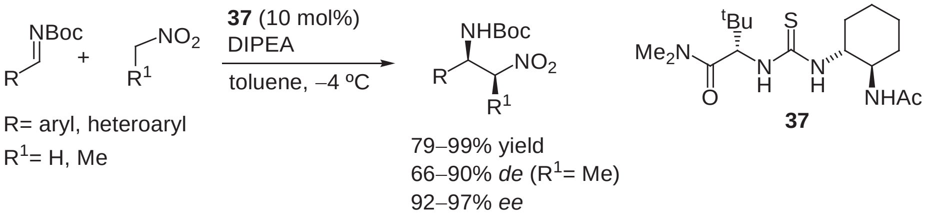


Figure 29.4 Representative dual and single hydrogen bond donor-based catalysts.

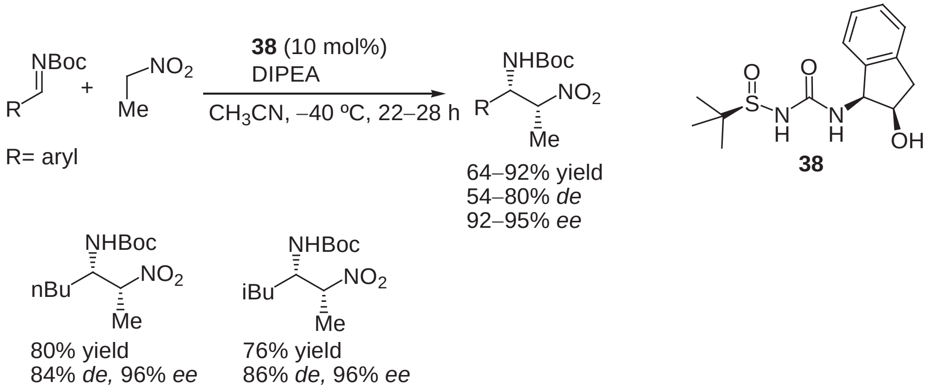
Figure 29.4 shows several structures with hydrogen bond donor capacity, all of which have been successfully employed as catalysts in asymmetric aza-Henry reactions. Compounds **37–39** represent neutral species featuring a (thio)urea moiety with an accompanying additional H-bond donor site, that is, acetamido, carbinol, and a second thiourea, respectively. Compounds **40–44** represent stronger BAs featuring a protonated bis-amidine or a phosphoric acid group; while **45** features a central guanidinium salt flanked by two thiourea groups. Given that these catalysts lack any basic site capable of activating the nitroalkane pronucleophile, addition of an external base as co-catalyst is often required.

The first aza-Henry reaction promoted by a hydrogen bond donor-based catalyst, that is, thiourea **37**, was described by Jacobsen in 2005 [45]. The addition reaction of nitromethane and nitroethane to aryl *N*-Boc imines in the presence of catalyst **37** and diisopropylethylamine (DIPEA) proceeds in very good yields and high diastereo- and enantioselectivity (Scheme 29.20).



Scheme 29.20 Chiral thiourea **37** catalyzed aza-Henry reaction.

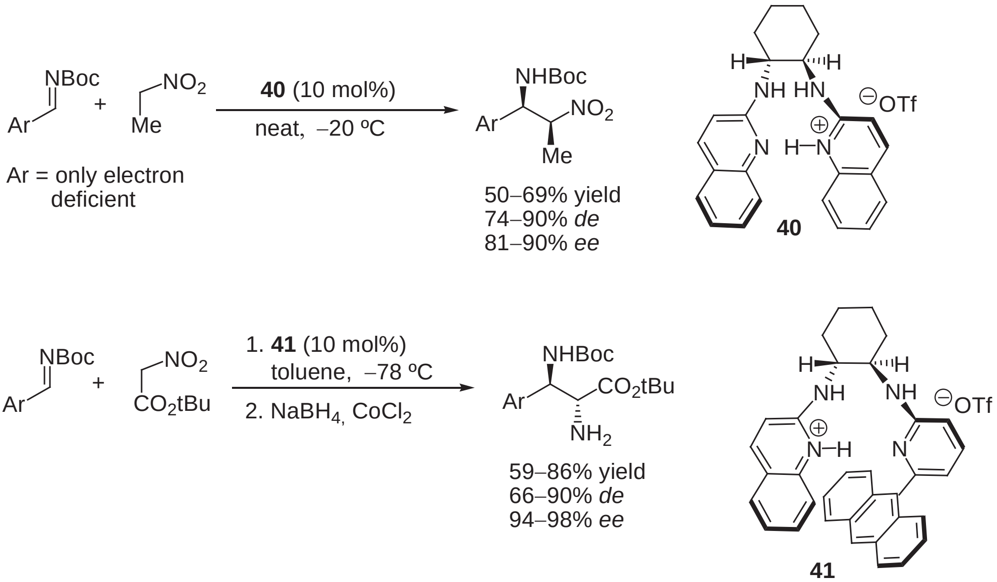
A similar reaction mechanism could be assumed for the aza-Henry reaction catalyzed by urea **38** [46]. In this particular case, the sulfinyl group acts both as an acidifying agent and a chiral controlling element, and allows the stereoselective addition of nitroethane to aromatic and, in two instances, aliphatic *N*-Boc imines (Scheme 29.21).



Scheme 29.21 Chiral **38** catalyzed aza-Henry reaction.

On the other hand, results obtained in the addition of nitromethane to aryl *N*-Boc imines in the presence of triethylamine and using catalyst **39** (ee 65–91%) seem to indicate that the incorporation of two thiourea groups in a chiral platform, BINAM-based **39**, neither improves the stereochemical outcome of the reaction nor the catalyst activity, even with higher catalyst loading (20 mol%). Only the single-step synthesis of the catalyst **39** from commercially available materials could represent an advantage [47].

In contrast to catalysts **37–39**, which are neutral species with dual hydrogen bond donor capability, catalysts such as **40–43** are ionic displaying a hydrogen bond donor site that better resemble the proton (H^+), which is probably the most common Lewis acid found in Nature. The pioneering work carried out by Johnston showed the effectiveness of the chiral proton-based structure **40** in the addition of nitromethane and nitroethane to aryl *N*-Boc imines (Scheme 29.22) [48]. As a

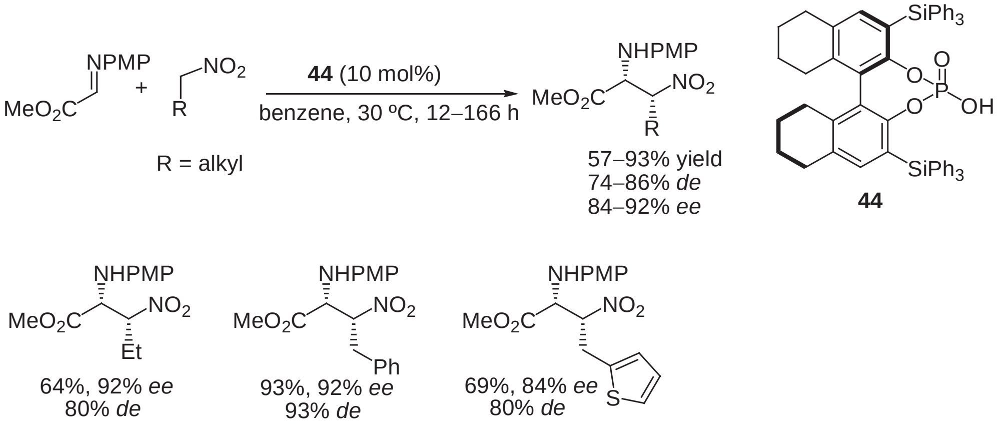


Scheme 29.22 Enantioselective aza-Henry reactions of *N*-Boc imines catalyzed by **40** and **41**.

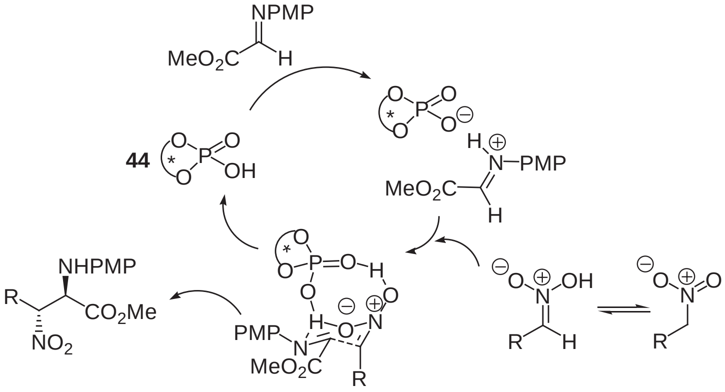
limitation, electron-deficient imines were required to obtain moderate yields and enantioselectivities (R = Ph, 57% yield, 60% ee). A second-generation catalyst, such as **41**, allowed improved results and scope – the aza-Henry reaction between various aryl *N*-Boc imines and α-nitroesters, to produce substituted glycines, proceeded in high yield and enantioselectivity [49].

Catalyst **40** and **41** have been employed in the synthesis of α-substituted *anti*-α,β-diamino phosphonic acid derivatives [50] and β-amino acids [51], respectively. Subsequent modifications of the reaction conditions and catalyst structure (catalyst **42** in Figure 29.4) allowed also the synthesis of α-substituted *syn*-α,β-diamino acid derivatives of phenylalanine [52]. Further studies, aimed at improving catalyst **40** activity by addition of over-stoichiometric amounts of triflic acid, led to catalysts such as **43**, which showed increased effectiveness in promoting the addition of unactivated nitroalkanes to either electron-poor or -rich aryl *N*-Boc imines [53]. Although it seems that this type of catalysis is performed by activation through hydrogen bond, the concurrent intervention of the basic nitrogen of the quinoline moiety could not be ruled out.

A purely ionic hydrogen bond activation mechanism might be involved in the aza-Henry reaction between α-iminoesters, a very reactive subclass of imines, and various nitroalkanes catalyzed by the BINOL phosphoric acid **44** [54]. The corresponding β-nitro-α-amino acid esters were produced in good yields, diastereo- and enantioselectivities (Scheme 29.23). The authors postulated a dual role of catalyst **44** through activation of the α-iminoester by protonation and control over the nitroalkane/nitronate equilibrium (Scheme 29.24).

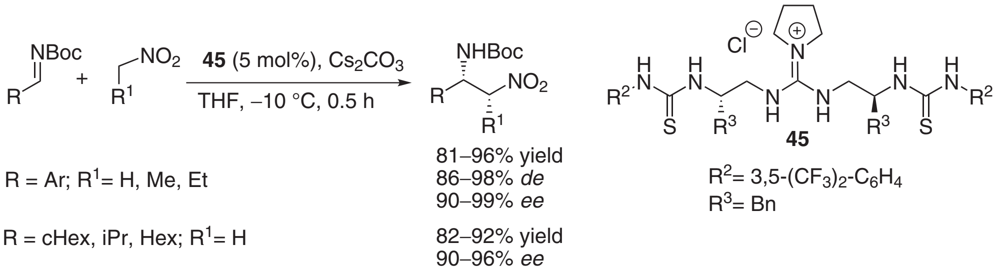


Scheme 29.23 Enantioselective aza-Henry reaction of α-iminoesters catalyzed by **44**, and representative examples.



Scheme 29.24 Proposed reaction mechanism involving catalyst **44**.

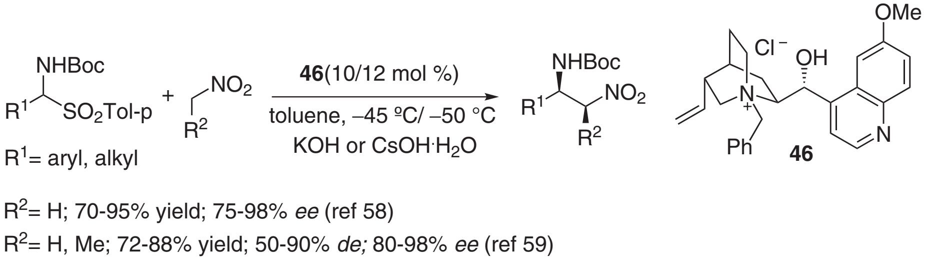
On the other hand, chiral guanidinium salt **45** catalyzes the addition of nitromethane and nitroethane to *N*-Boc imines with very good yields and excellent stereoselectivity. The reactions, which require stoichiometric Cs_2CO_3, proceed under smooth conditions (THF, −10 °C) within extremely short times compared to other procedures (Scheme 29.25) [55]. While detailed description of the mechanistic scenario is unknown, it seems that, again, imine activation through H-bonding to the catalyst is central, as catalysts lacking the thiourea groups did not show any asymmetric induction.



Scheme 29.25 Enantioselective aza-Henry reaction of *N*-Boc imines catalyzed by **45**.

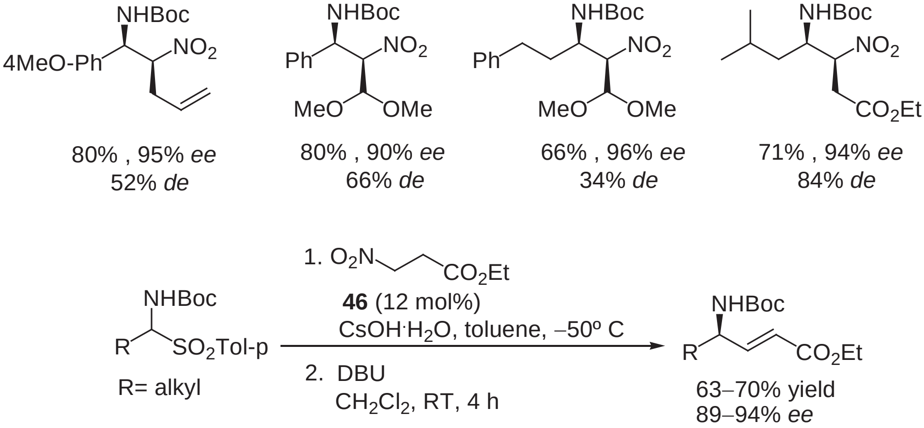
29.2.3
Phase-Transfer Conditions (PTC)

Asymmetric catalysis effected by a chiral salt, typically a quaternary ammonium species, under basic conditions in a biphasic system (phase-transfer conditions) has found wide application in recent years [56]. These conditions are particularly amenable for aza-Henry reactions: on the one hand, the nitroalkane pronucleophile requires a base to become a nitronate, which is the actual nucleophile in the reaction, and, on the other hand, *N*-acyl or *N*-sulfonyl imines can be generated by base-promoted elimination of sulfinic acid from the precursor α-amido sulfones, which are bench-stable compounds. This latter route for *in situ* generation of imines is very convenient [57] since even the reluctant enolizable aldehyde derived imines can be smoothly generated. In fact, the first catalytic asymmetric aza-Henry protocol amenable to enolizable aldehyde-derived azomethine substrates was achieved employing this type of catalysis, by generating *N*-carbamoyl imines *in situ* from α-amido sulfones in the presence of cinchona derived PTC catalysts. The groups of Herrera and Bernardi [58], and Palomo [59] simultaneously described the effectiveness of the commercial *N*-benzyl-quininium chloride **46** as PTC catalyst in the addition of nitromethane [58, 59] and nitroethane [59] to *in situ* generated *N*-Boc imines (Scheme 29.26). The presence of inorganic base (KOH and $CsOH \cdot H_2O$, respectively) is a requirement and the enantiomeric excesses were generally high for aryl substituted α-amido sulfones, but most importantly regularly above 94% for enolizable aldehyde-derived azomethines.

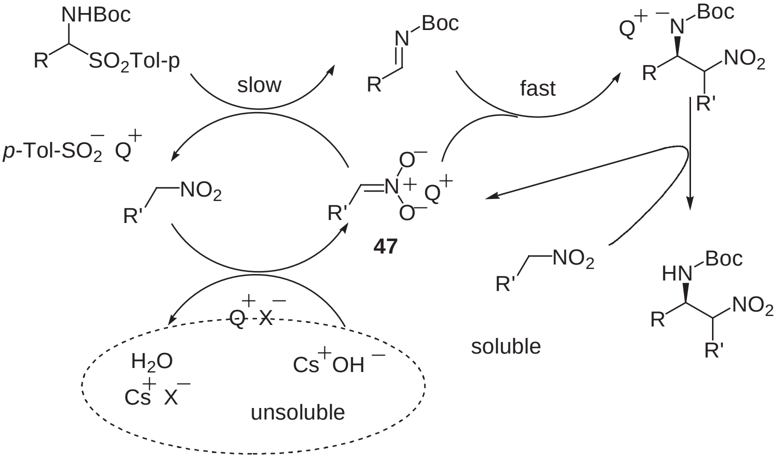


Scheme 29.26 Asymmetric aza-Henry reaction of nitromethane and nitroethane under PTC conditions.

In a later work, the suitability of this methodology for a range of functionalized nitroalkane substrates was demonstrated (Scheme 29.27) [60]. More interestingly, a new asymmetric synthesis of γ-amino α,β-unsaturated esters was realized through a catalytic, highly enantioselective formal addition of β-acryloyl anion equivalents to azomethines. The authors postulated a catalytic cycle based on experimental observations and quantum calculations, in which the chiral nitronate **47** is the nucleophile, but also acts as a base that promotes the *in situ* generation of the *N*-acyl imine (Scheme 29.28). A concise enantioselective synthesis of L-(−)-733,061, a NK-1 tachykinin receptor antagonist, has been achieved employing the current catalytic enantioselective aza-Henry reaction as the key step [61].



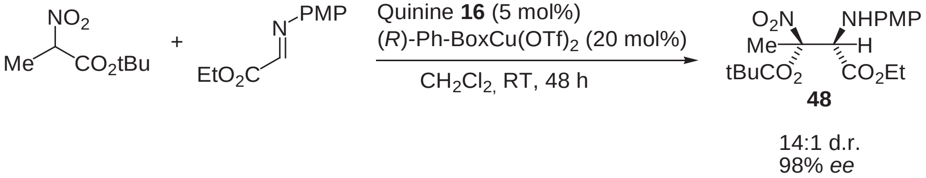
Scheme 29.27 Representative β-nitroamines synthesized and formal catalytic enantioselective 2-ethoxycarbonylvinylation of *N*-acyl imines.



Scheme 29.28 Proposed mechanism for the aza-Henry reaction involving α-amido sulfones under chiral PTC conditions.

29.2.4
Miscellaneous

A hybrid strategy that involves synergism between metal catalyst and BB organocatalyst has been applied to the aza-Henry reaction [62]. Thus, the aza-Henry reaction between *tert*-butyl 2-nitropropionate and iminoesters is catalyzed by combined use of quinine (**16**) and a Cu-bisoxazoline catalyst (20 mol%). The approach is based on chiral molecular recognition of the organic and the metallic catalysts and produces the densely functionalized adduct **48** in good diastereo- and enantioselectivity (Scheme 29.29).



Scheme 29.29 Enantioselective aza-Henry reaction leading to quaternary stereocenters by combining BB/metal catalysis.

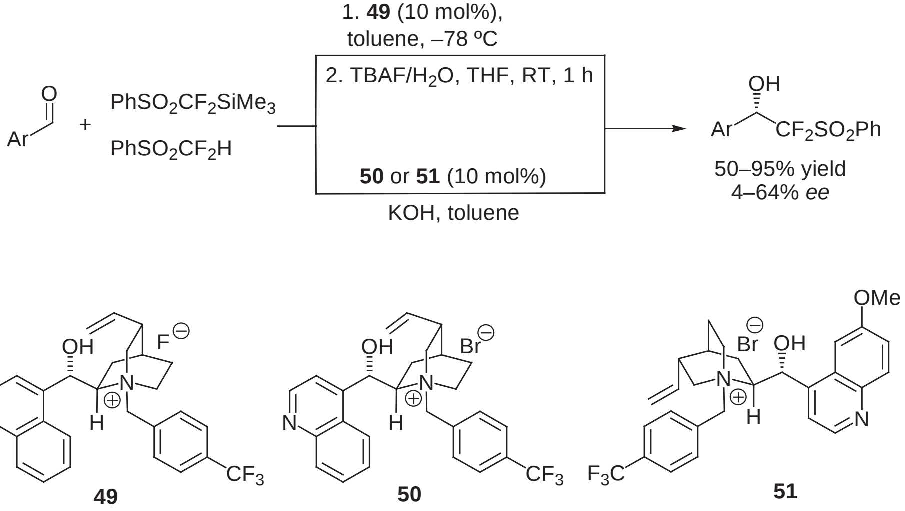
29.3
Organocatalytic Addition of Sulfones to C=X

29.3.1
Introduction

The use of sulfones in asymmetric catalysis has received increased attention in recent years [63], in part because the electron-withdrawing character of the sulfone group enhances the electrophilicity of an adjacent C=C double bond or the acidity of an adjacent C–H pronucleophile. Another reason is the capability of the sulfone functionality to be removed in an ulterior step under smooth reductive conditions (hydrodesulfonation) to give alkyl units [64].

29.3.2
Organocatalytic Addition of Sulfones to C=O

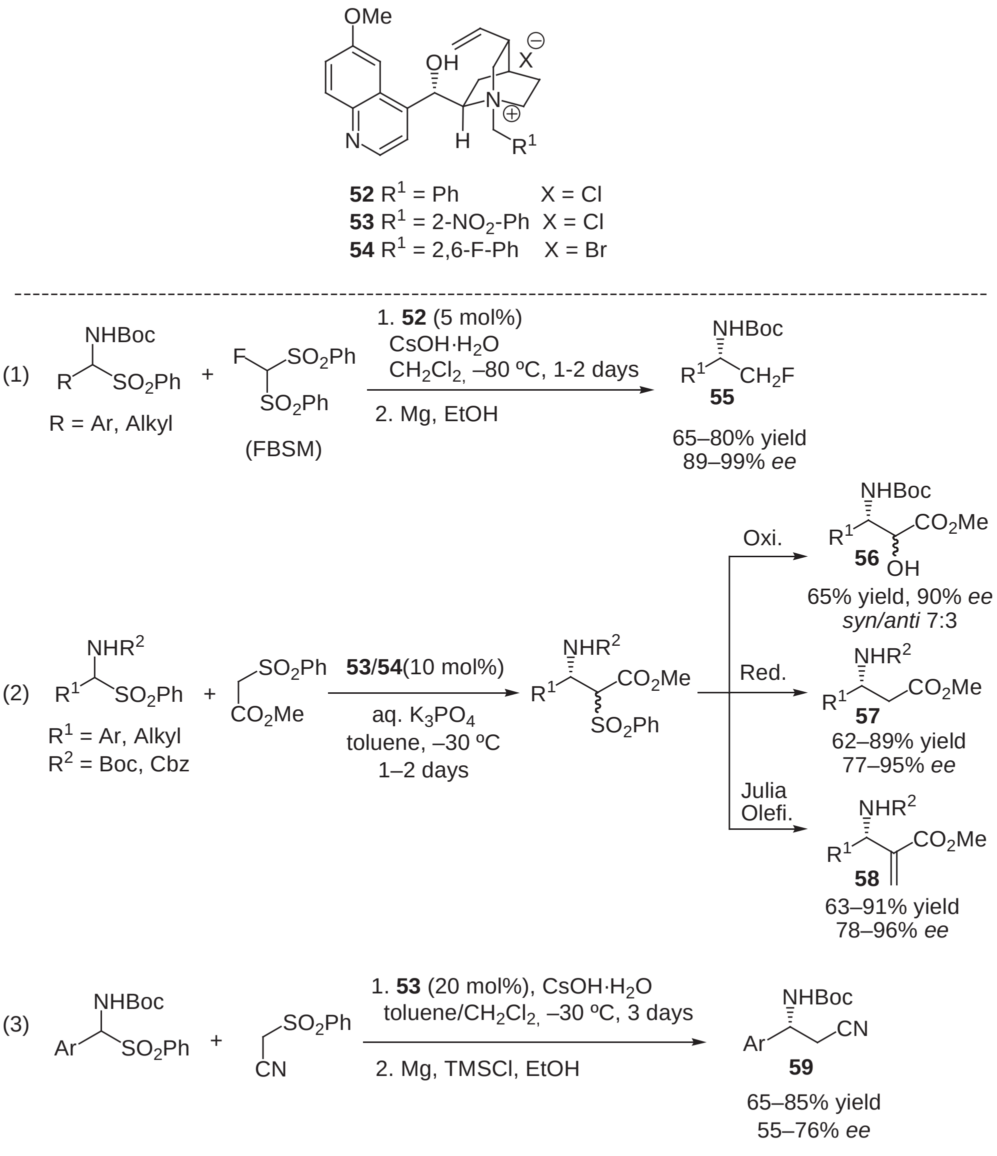
The 1,2-addition of sulfone-containing nucleophiles to aldehydes is a highly valuable tool in synthetic chemistry. However, since the first addition of α-chlorophenylsulfone to aromatic aldehydes under PTC in 1998 [65], only one further approach has been reported. Hu *et al.* reported the enantioselective 1,2-addition of $Me_3SiCF_2SO_2Ph$ and $PhSO_2CF_2H$ to aromatic aldehydes catalyzed by a chiral alkaloid-based quaternary ammonium salt (Scheme 29.30) [66]. Several chiral ammonium salts were screened and the best results were obtained with cinchonine and quinine derivatives. Interestingly, for the reactions promoted by quinine derivative **51** relatively high temperatures were necessary to achieve good enantioselectivities and yields. The reactions work only with aromatic aldehydes and provide the corresponding addition products in yields and enantioselectivities from poor to moderate (Scheme 29.30).



Scheme 29.30 Catalytic asymmetric aldol reaction of sulfone-derived compounds with aromatic aldehydes.

29.3.3
Organocatalytic Addition of Sulfones to C=N

Three different highly enantioselective addition reactions of sulfones to *in situ* generated *N*-Boc and *N*-Cbz imines have been reported recently, all under PTC using structurally similar chiral ammonium salts as catalysts (Scheme 29.31). In 2007, Shibata, Toru, and coworkers developed a PTC reaction of imines, generated *in situ* from α-amido sulfones, with 1-fluorobis(phenylsulfonyl)methane (FBSM) [67]. A quinidine derived quaternary ammonium chloride (**52**) is used as catalyst, and the Mannich-type reaction proceeds smoothly to afford the 1-fluorobis(phenylsulfonyl)methylated amines in high yields and excellent enantioselectivities. Desulfonation of adducts by treatment with Mg in EtOH yields the monofluoromethylated adducts **55** with nearly complete retention of the enantiomeric excess [Scheme 29.31 (1)].

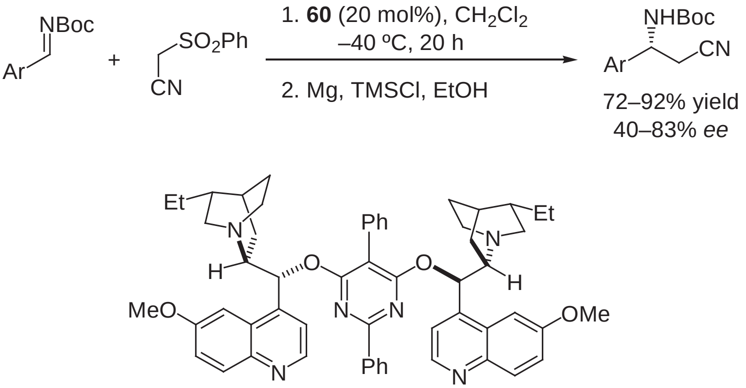


Scheme 29.31 Catalytic asymmetric Mannich reaction of sulfone-derived compounds under PTC conditions.

Ricci, Bernardi and coworkers demonstrated that asymmetric addition of arylsulfonylacetates to both *N*-Boc and *N*-Cbz imines can also be conducted very efficiently when using quinidine derivatives of type **53** and **54** as a catalyst [68]. These asymmetric Mannich-type reactions require toluene at –30 °C, aqueous K_3PO_4 as the base, and 10 mol% of the quaternary ammonium salt for optimal results. This organocatalytic approach is a practical procedure for the preparation of β-amino-α-hydroxy esters **56**, β-amino esters **57**, and aza-Morita–Baylis–Hillman products **58** upon oxidative or reductive desulfonylation or Julia-type olefination of adducts, respectively [Scheme 29.31 (2)].

The third procedure, reported by the Palomo group, consists of the nucleophilic addition of 2-(phenylsulfonyl)acetonitrile to *in situ* generated *N*-Boc imines catalyzed by **53** [69]. Although moderate enantiomeric excesses (up to 76%) were obtained, the methodology allowed for the simple synthesis of enantioenriched α-unsubstituted β-aminonitriles **59** [Scheme 29.31 (3)].

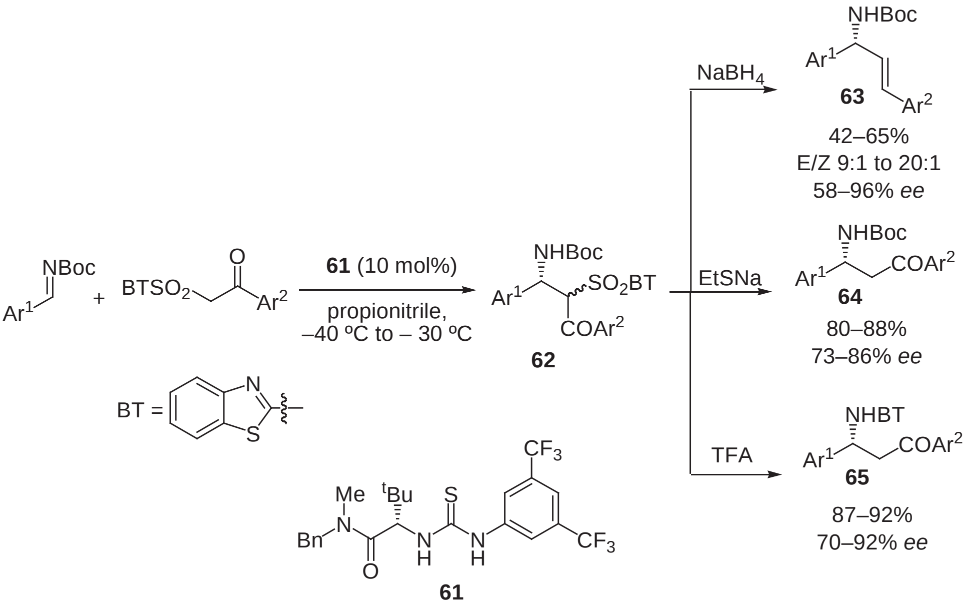
In addition, Palomo's group explored the use of chiral Brønsted bases such as **60** as an alternative approach for the addition of (phenylsulfonyl)acetonitrile to *N*-Boc-imines (Scheme 29.32). Only aromatic imines provide the desired final adducts in good yields, albeit with variable optical purities [69].



60 [DHQ]$_2$PYR

Scheme 29.32 [DHQ]$_2$PYR catalyzed addition of β-sulfonyl acetonitrile to *N*-Boc imines.

In 2009, the Jørgensen group developed the organocatalytic asymmetric addition of β-keto-benzothiazole-sulfones to *N*-Boc aromatic imines based on the thiourea organocatalyst **61** and using as solvent, unusually, propionitrile (Scheme 29.33) [70]. The reaction proceeds with moderate yields, and stereoselectivities from moderate to excellent. The initially formed adducts **62** were easily transformed into different types of protected amines like the allylic amines **63**, or β-amino ketones **64** and **65**.



Scheme 29.33 Thiourea **61** catalyzed addition of heteroaryl β-ketosulfones to *N*-Boc imines.

29.4
Summary and Outlook

This chapter covers the most fundamental developments in the organocatalytic addition reaction of nitroalkyls and sulfones to C=X that have been documented in recent years, along with major mechanistic implications. Discussion includes the limitations of the present protocols, identifies the most salient gaps, and gives the prospects for future improvements and applications. The organocatalyzed asymmetric addition of nitroalkyls to azomethine groups has been most widely explored in comparison to the Henry reaction. Despite the advances in the field, most methods are limited to nitromethane and those involving longer chain or functionalized nitroalkanes are little explored and generally lead to a poor control of the *syn/anti* stereoselectivity. Regarding the organocatalytic and asymmetric addition of sulfones to C=X groups, only a few examples have been reported and the development of new processes is clearly needed to realize the potential of the approach in synthesis.

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30
Hydrocyanation and Strecker Reactions

Carsten Kramer and Stefan Bräse

30.1
Introduction

In 1850, A. Strecker accidently accomplished the first synthesis of the amino acid alanine by mixing of acetaldehyde, ammonia, and HCN and subsequent hydrolysis of the formed adduct [1]. Whereby this three-component-reaction is in general known as the Strecker reaction, the addition of a cyanide source to a preformed imine species is often referred to as the "modified Strecker reaction," The so-formed α-amino nitriles, or from cyanide addition to carbonyl compounds the so-obtained cyanohydrins, are versatile building blocks that can be converted, for example, into α-hydroxy carbon acids, amino acids, amino alcohols and diamines.

30.1.1
Overview

Several catalysts have been developed for the asymmetric organocatalyzed hydrocyanation of carbonyls and for the Strecker reaction. This chapter divides the catalysts into several subgroups, defined according to important structural motifs responsible for catalytic activity. Each catalyst group will be discussed in detail with regard to substrate scope, limitations, and other important factors. In addition, mechanistic insights will be provided, if transition states are satisfyingly revealed by experimental work or *in silico* studies.

30.2
Amino-Acid Containing Catalysts for Carbonyl Hydrocyanation

In 1981, Inoue and coworker accomplished the first organocatalyzed hydrocyanation of benzaldehyde (**1**) with reasonable asymmetric induction (Scheme 30.1) [2]. By using 2 mol% of the cyclic dipeptide *cyclo*(L-phenylalanine-L-histidine) (**2**), benzaldehyde (**1**) reacted with HCN in benzene at 35 °C to give the cyanohydrin **3**

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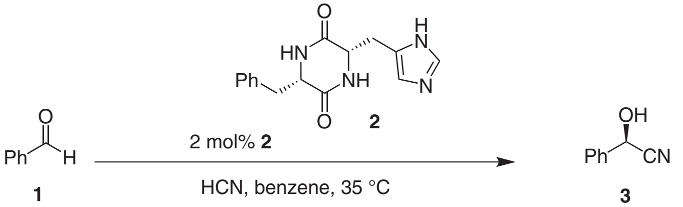
with high enantiopurity (90% ee at 40% conversion). The ee values diminished with prolonged reaction times (12% ee at 90% conversion).

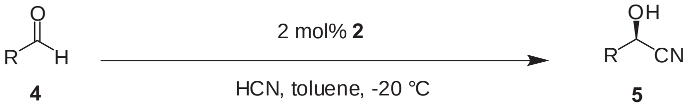


90%*ee* at 40% conversion
12%*ee* at 90% conversion

Scheme 30.1 Asymmetric hydrocyanation using Inoue's catalyst **2**.

The enantioselectivity at higher conversion rates could be further improved by shifting the solvent to toluene and by lowering the reaction temperature to −20 °C (Table 30.1) [3]. Under optimized conditions, cyanohydrins **5** were obtained from various aromatic (entries 1, 2; 57–97% yield; 78–97% ee) and aliphatic (entries 5, 6; 44–79% yield; 18–71% ee) substrates **4**. Heteroaromatic compounds were found to be problematic (entry 4; 60% yield; 42%) and benzaldehydes substituted with electron-withdrawing groups were incompatible substrates, providing low enantioselectivities (entry 3, quant. yield; 32% ee). To explain the stereoinduction it was reasoned that HCN protonates the imidazole moiety of **2**, while the aldehyde oxygen of **1** is hydrogen-bonded to the diketopiperazine. Thus, the cyanide anion is pre-coordinated at the imidazolium ion for the attack at the carbonyl function of **4**. Elucidation of the actual mechanism and the influencing factors for high enantioselectivities were a formidable challenge for several research groups and a satisfying overall picture has not yet been obtained (for an overview of studies see

Table 30.1 Hydrocyanation of aldehydes promoted by diketopiperazine **2**.



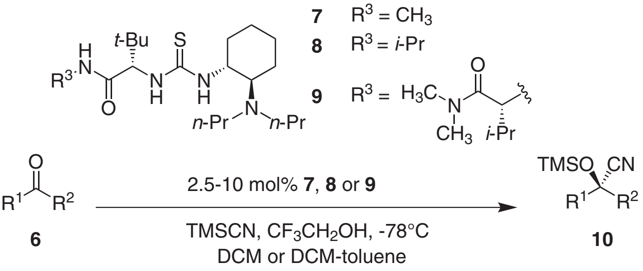
Entry	R	Time (h)	Yield (%)	ee (%)
1	Ph	8	97	97
2	4-MeO-Ph	10	57	78
3	4-CN-Ph	8	Quantitative	32
4	2-Furyl	8	60	42
5	*i*-Pr	5	79	71
6	2-Me-propyl	5	44	18

Reference [4]). Chiral hydantoins could also be applied as catalysts for carbonyl hydrocyanation, but the enantiopurities were lower [5–7].

30.3
Thiourea Catalysts for Carbonyl Hydrocyanation

In 2005, thiourea catalyst **7** was proved to be an efficient and recyclable catalyst for the cyanosilylation of various ketones **6** (Table 30.2) [8]. In the reaction with 5 mol% catalyst **7**, TMSCN, and an alcoholic additive, aryl–alkyl (entries 1, 3–5), alkenyl–alkyl (entries 10, 11) ketones, and cyclic ketones (entry 12) afforded adducts in high yields (91–98%) and high enantiopurities (86–98% ee). Yields for heteroaromatic analogues were lower (81–88%) but with high enantioselectivities (97–98% ee) (entries 6, 7). The substrate scope could be also extended to aldehydes

Table 30.2 Hydrocyanation of ketones supported by thiourea catalysis.

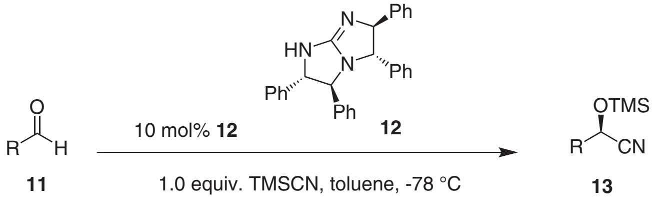


Entry	R^1	R^2	Catalyst (concentration, mol%)	Time (h)	Yield (%)	ee (%)
1	Ph	*i*-Pr	**7** (5)	24	97	86
2	Ph	*i*-Pr	**8** (5)	60	91	95
3	4-Me-Ph	Me	**7** (5)	36	96	98
4	1-Naphthyl	Me	**7** (5)	36	91	95
5	2-Naphthyl	Me	**7** (5)	12	98	97
6	2-Furyl	Me	**7** (10)	48	81	97
7	2-Thienyl	Me	**7** (10)	48	88	98
8	2-Pyridyl	Me	**8** (5)	12	97	96
9	2,4,5-Trifluoro-Ph	Me	**8** (5)	12	90	90
10	(*E*)-2-Ph-ethenyl	*n*-Bu	**7** (5)	12	97	93
11	(*E*)-Pent-1-enyl	Me	**7** (5)	48	95	89
12	2-Bromocyclohex-2-enone		**7** (5)	12	95	97
13	Ph	H	**7** (1)	2	61	96
14	(*E*)-2-Ph-ethenyl	H	**7** (1)	2	69	93
15	Bn	Me	**9** (5)	18	95	85
16	Methoxymethyl	Me	**9** (2.5)	8	81	88

(entries 13, 14), but application to dialkyl ketones was impossible. Studies on catalyst **7** using kinetic analysis, NMR experiments as well as DFT calculations gave hints for the geometry of the transition state and the basis for enantio-induction [9]. The data are consistent with a ternary transition structure out of **7**, ketone **6**, and HCN (from TMSCN/CF_3CH_2OH) and that catalysis of **7** involves both the tertiary amine and the thiourea moiety, which presumably interacts with **6** over hydrogen-bonds. It could be shown that steric and electronic interactions of substrate **6** with the amino-acid portion of catalyst **7** results in high enantio-induction. To accentuate these interactions, catalysts **8** and **9** were designed bearing sterically more demanding substituents. Catalyst **8** showed improved results (compare entries 1 and 2), especially for the cyanosilylation of electron-deficient and sterically demanding aromatic substrates (entries 8, 9), whereas catalyst **9** afforded adducts of the problematic dialkyl ketones substrates (entries 15, 16). Remarkably, dialkyl ketones bearing a π or lone pair substituent gave higher enantioselectivities, suggesting that the source of asymmetric induction is more electronic, rather than due to steric interactions.

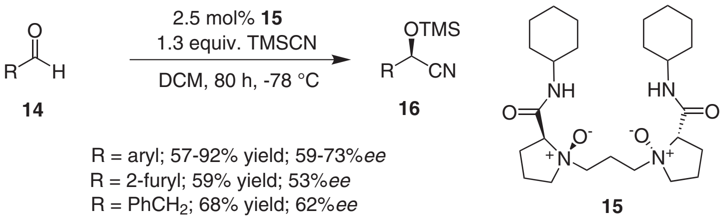
30.4
C_2-Symmetrical Guanidines and *N,N′*-Dioxides

In 2002, a C_2-symmetrical bicyclic guanidine **12** (Scheme 30.2) was successfully used to for the cyanation of aliphatic aldehydes **11** to give (*R*)-cyanohydrins **13** in quantitative yields and reasonable enantioselectivities (60–70% ee) [10]. The use of ketones resulted in lower enantioselectivities.


10 mol% 12
12
11
1.0 equiv. TMSCN, toluene, -78 °C
OTMS
R
CN
13
R = aliphatic; quant. yield; 60-70%ee

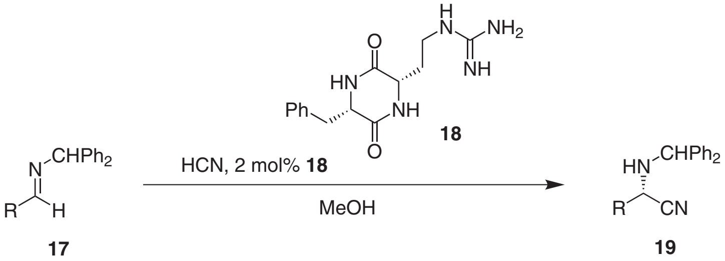
Scheme 30.2 Application of a C_2-symmetrical bicyclic guanidine as catalyst.

In addition, *N,N′*-dioxide **15** could sufficiently support the silylcyanation of aldehydes **14** (Scheme 30.3) [11]. Aromatic aldehydes gave corresponding adducts in moderate to high yields (57–92%) and reasonable optical purities (59–73% ee); for heterocyclic and aliphatic substrates the results were lower (59–68% yield; 53–62% ee).


2.5 mol% 15
1.3 equiv. TMSCN
DCM, 80 h, -78 °C
14
16
15
OTMS
CN
R = aryl; 57-92% yield; 59-73%ee
R = 2-furyl; 59% yield; 53%ee
R = PhCH2; 68% yield; 62%ee

Scheme 30.3 Silylcyanation supported by L-proline derived *N*,*N*′-dioxides.

Table 30.3 Asymmetric Strecker reaction supported by diketopiperazine catalysis.



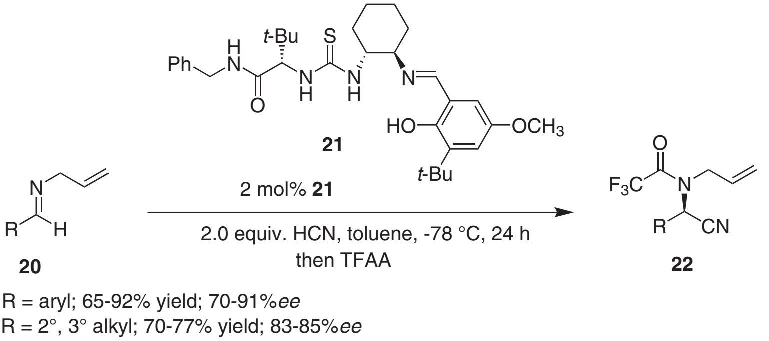
Entry	R	Temperature (°C)	Yield (%)	ee (%)
1	Ph	−25	97	>99
2	4-Cl-Ph	−75	94	>99
3	4-MeO-Ph	−75	90	96
4	3-NO_2-Ph	−75	71	<10
5	2-Furyl	−75	94	32
6	*t*-Bu	−75	80	17

30.5
Diketopiperazines as Catalysts for the Strecker Reaction

Inspired from the usage of cyclic peptides for the hydrocyanation of carbonyls, cyclic peptides were applied to the Strecker reaction (Table 30.3) [12, 13]. Employment of **2** to the mechanistically similar Strecker reaction did not provide any asymmetric introduction: In the reaction of benzaldehyde (**1**) catalyzed by **2**, proton transfer takes place from HCN to the imidazole residue in **2**. The resulting imidazolium ion can serve as an acid catalyst for the asymmetric cyanation of **1**; meanwhile, in the case of the Strecker reaction, the more basic benzaldimine (**17**) becomes protonated directly by HCN without interaction with the catalyst [4]. Thus, replacement of the imidazole function with the more basic guanidine turned out to be required for high asymmetric introduction. On doing this, *N*-benzhydryl-protected α-amino nitriles **19** could be obtained in high ee's and yields from the aldimines **17** using the guanidine catalyst **18**. Excellent results were provided for substituted benzylic aldimines (entries 1–3), whereby the 3-nitro-derivative (entry 4), electron-deficient aromatic (entry 5) and aliphatic substrates (entry 6) afforded an unsatisfactory outcome. In general, N-protecting groups are essential for the enantioselective Strecker reaction, because unprotected α-amino nitriles are configurationally unstable [4]. For further functionalization, the benzhydryl-protecting group is most suitable because α-amino nitriles so protected can be transformed into the corresponding amino acids without loss of optical purity by applying literature conditions [14]. The mechanism of catalyst **18** might be different from that of catalyst **2**: cyanohydrin synthesis with **2** is performed as a gel in toluene and asymmetric induction is eliminated in methanol [4]. In contrast, the reactions catalyzed by **18** are homogeneous and in methanol. Remarkably, catalysts **2** and **18** contain all (*S*)-amino acids, but cyanide addition occurs from enantiotopic faces of the substrates, leading to formation of (*R*)-cyanohydrins versus formation of (*S*)-amino-nitriles [4].

30.6
(Thio)urea Catalysts for the Strecker Reaction

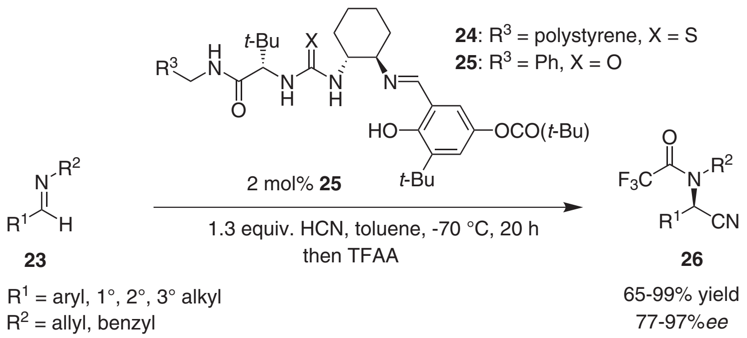
Through the synthesis of parallel combinatorial libraries, Jacobsen and coworker discovered a new class of catalysts for the Strecker reaction [15]. Because of its modular assembly, the new catalyst type was amenable to solid-phase synthesis and fast preparation, screening, and lead optimization were feasible. The best catalyst candidate afforded the Strecker product from *N*-allylbenzaldimine in 78% yield and 91% ee. Catalyst **21** was prepared as the soluble variant of the optimized candidate and proved to be an effective catalyst for a range of imine derivates **20**, affording aromatic amino nitriles **22** in moderate to good yields (65–92%) and high enantioselectivities (70–91% ee) (Scheme 30.4). In addition, aliphatic aldimines **20**


Ph
H
N
O
t-Bu
S
N
H
N
H
N
HO
OCH3
t-Bu
21
N
R
H
20
2 mol% 21
2.0 equiv. HCN, toluene, -78 °C, 24 h
then TFAA
O
F3C
N
R
CN
22
R = aryl; 65-92% yield; 70-91%ee
R = 2°, 3° alkyl; 70-77% yield; 83-85%ee

Scheme 30.4 Hydrocyanation using Jacobsen's Schiff-base catalyst **21**.

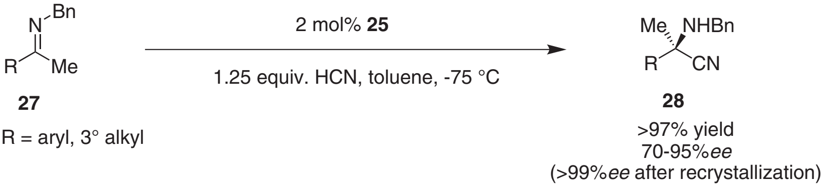
underwent hydrocyanation in good yields with >80% ee. Among these remarkable results, usage of the allyl protecting group necessitated subsequent amidation with TFAA (trifluoroacetic anhydride) because of the known configurative instability of *N*-allyl α-amino nitriles.

For better enantiopurities with aliphatic substrates, structural elements crucial for a high stereoinduction were revised by library screening on a solid phase. It was found that the presence of a bulky substituent at both the amino acid and at the 3-position of the salicylimine moiety were key elements responsible for high enantioselectivity. By employing of a pivaloyl substituent at the 5-position of the salicylaldehyde moiety, **24** was found to be a superior catalyst for the Strecker reaction of aliphatic imines **23** (Scheme 30.5) [16]. By adaptation of solid-supported **24** to homogenous conditions, the thiourea was replaced with a urea moiety because of the more convenient synthesis. By applying the so-synthesized catalyst **25**, Strecker adducts **26** were obtained in high ee's and yields. Transformation of 3,4-dihydroisoquinoline, a fixed (*Z*)-imine, into the Strecker adduct (in 88% yield; 91% ee) showed that no difference in asymmetric introduction existed, whether (*E*)-isomers or the (cyclic) (*Z*)-isomer of the imine was used. Although application of the soluble catalyst **25** led to 2–4% higher ee's the use of the resin-bound analog **24** is more practical since the catalyst can be removed by simple filtration and be reused several times with no remarkable loss of catalyst reactivity or product enantioselectivity.



Scheme 30.5 Strecker reaction supported by resin-bound and soluble catalysts.

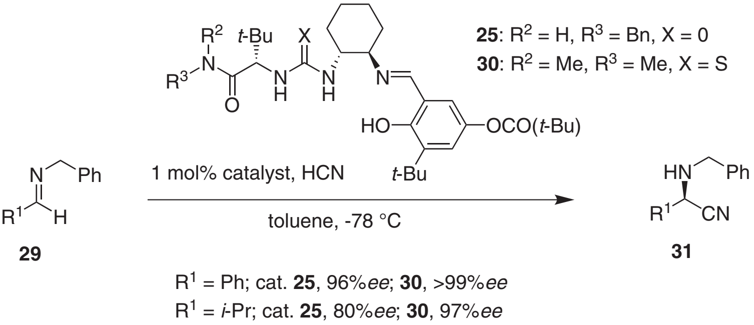
Since there is great interest in compounds bearing quaternary stereocenters, soluble catalyst **25** was also applied to keto-imines in the presence of *in situ* generated HCN (Scheme 30.6) [17]. Whereas hydrocyanation adducts of *N*-allyl protected ketimines were prone to decompose via a retro-Strecker reaction, *N*-benzylated Strecker adducts **28** were obtained in mostly excellent yields and very high ee's. In general, acetophenone imines **27** were suitable substrates whereas aliphatic ketimines **27** showed a lowered optical purity. Although the benzyl protection group was necessary to obtain stable Strecker adducts **28**, transformation of these adducts into amino acids was made more difficult. It could also be shown that catalyst **25** is recyclable without loss of activity or selectivity. Further attempts also led to an improved high-yielding and easy performable synthesis of soluble catalyst **25** [18].


Bn
N
R
Me
27
R = aryl, 3° alkyl
2 mol% 25
1.25 equiv. HCN, toluene, -75 °C
Me
NHBn
R
CN
28
>97% yield
70-95%*ee*
(>99%*ee* after recrystallization)

Scheme 30.6 Hydrocyanation of keto-imines **27** by urea catalyst **25**.

To reveal the precise role of catalyst **25** in the Strecker reaction, several observations were taken into account [19]: (i) NMR experiments proved that the catalyst adopted a well-defined and solvent-independent secondary structure; (ii) hydrocyanations with catalyst **25** obeyed Michaelis–Menten kinetics, with a first-order dependence on catalyst and HCN, and saturation kinetics with respect to the imine substrate; (iii) these results implicated the reversible formation of an imine–catalyst complex, whereby structure–selectivity experiments of modified catalyst analogues showed that hydrogen bonds from the urea unit of the catalyst to the imine substrate were the solely relevant attractive interactions; (iv) titration experiments of *N*-*p*-methoxybenzyl-acetophenone imine [present in a equilibrium of (*Z*)- and (*E*)-imine] with catalyst **25** showed that only NMR signals of the (*Z*)-imine were shifted. The experiment revealed in this way that the (*Z*)-isomer is the only matching isomer for catalyst **25**. This proposal is in accordance with the observation that 3,4-dihydrosioquinoline was a highly competent substrate for the Strecker reaction (see above). Further NMR experiments and computational calculations showed that in the catalyst–imine complex the (*Z*)-configurated imine is hydrogen bonded to both urea hydrogens simultaneously.

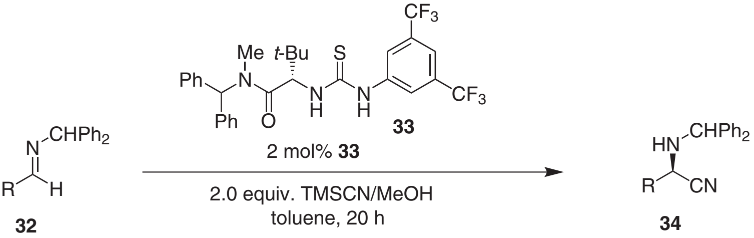
By merging all the above observations, the following conclusions about the scope and selectivity were made: (i) A large group on the substrate imine carbon is directed away from the catalyst. Aldimines with sterically less demanding substituents make the discrimination difficult, leading to poor selectivities. (ii) A small group on the imine (H for aldimines, Me for methyl keto-imines) points into the catalyst. This explains why keto-imines bearing larger substituents are poor substrates. (iii) The imine *N*-substituent is also directed away from the catalyst. Thus, the size of the N-protecting group is restricted because the (*Z*)-isomer of the imine has to be accessible. (iv) On basis of the observed sense of stereoinduction, hydrocyanation takes place over the diamine cyclohexane portion and away from the amino acid/amide portion. In consequence, replacing the secondary amide function of **25** with a bulkier tertiary amide led to higher enantioselectivities with catalyst **30** (Scheme 30.7). In addition, on replacing the urea with a thiourea functionality higher enantioselectivities were obtained, presumably due to beneficial electronic effects of the sulfur for the hydrogen bonds to the imine substrate. These rational designed structural changes led to catalyst **30**, which exhibited nearly perfect enantiocontrol even with previously problematic substrates. Further intensive studies on this catalyst revealed deeper insight into the role of certain structural elements [20].


R2
t-Bu
X
R3
N
N
H
N
H
O
N
HO
OCO(t-Bu)
t-Bu
25: R2 = H, R3 = Bn, X = O
30: R2 = Me, R3 = Me, X = S
N
Ph
R1
H
29
1 mol% catalyst, HCN
toluene, -78 °C
HN
Ph
R1
CN
31
R1 = Ph; cat. 25, 96%ee; 30, >99%ee
R1 = i-Pr; cat. 25, 80%ee; 30, 97%ee

Scheme 30.7 Development of the improved catalyst **30** by rational design.

Facing the requirements of large-scale application of the Strecker reaction, Jacobsen addressed these problems with the revised second-generation catalyst **33** (Table 30.4) [21]. Reactions using the old catalyst generation suffered from the need for cryogenic temperatures (below 0 °C) and used hazardous and expensive cyanide sources (TMSCN/MeOH or HCN). Synthesis of either soluble catalyst **25**

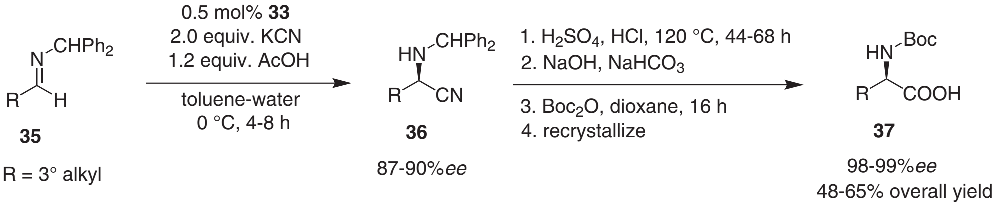
Table 30.4 Imine hydrocyanation using Jacobsen's second-generation thiourea catalyst.



Entry	R	Temperature (°C)	Yield (%)	ee (%)
1	*t*-Bu	−30	99	93
2	4-MeO-Ph	−30	99	99
3	4-Br-Ph	0	96	97
4	2-Thiophenyl	0	97	95
5	(*E*)-1-Me-pent-1-enyl	−30	98	91
6	*c*-Hex	−30	99	74

or resin-bound **24** required eight steps and the conversion of *N*-benzylated amino nitriles into the corresponding amino acids needed four steps. Therefore, the *N*-benzhydryl group is more suitable because there is no need for further acetylation or formylation of the Strecker adduct and, moreover, the so-protected α-amino nitrile is easily convertible into the amino acid. Catalyst **33** was found to catalyze the reaction of *N*-benzhydryl protected imines derived from alkyl (entry 1), aryl (entries 2, 3), heteroaryl (entry 4), and alkenyl aldehydes (entry 5) effectively. Imines with less sterically demanding substituents (entry 6) afforded only moderate ee's.

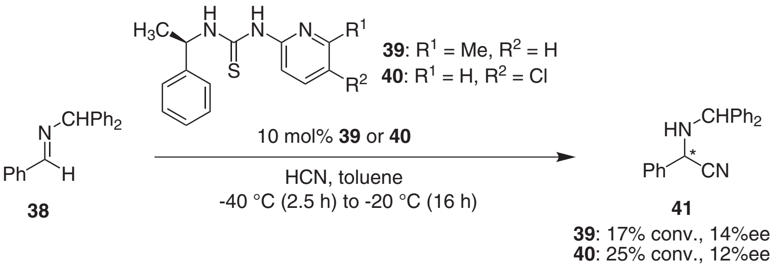
Owing to its structural simplicity, the synthesis of **33** proceeded in three steps on a multi-gram scale (74% overall yield on 5 g-scale). Using catalyst **33** it could be also proved that the multi-gram synthesis of industrial interesting unnatural amino acids (e.g., D-*tert*-leucine) is possible under biphasic conditions with only 0.5 mol% of **33** (Scheme 30.8). Aqueous KCN was used as a cheap and safer cyanide source, and this as well as the shortened reaction time and higher reaction temperature made this procedure more convenient for industrial application.



Scheme 30.8 Synthesis of unnatural amino acids on a multi-gram scale; Boc = *tert*-butoxycarbonyl.

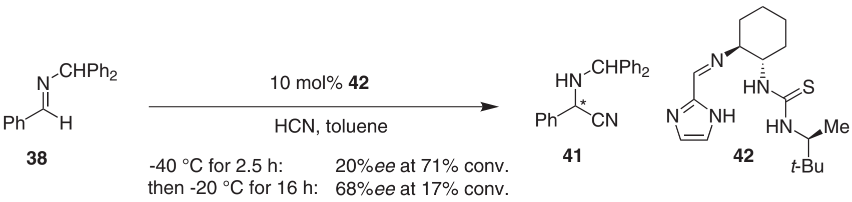
Intensive studies using NMR methods, kinetic experiments, and computational calculations were conducted to elucidate the catalytic mechanism and observed stereoinduction [22]. The data revealed that the hydrocyanation catalyzed by **33** presumably proceed over an initial amido-thiourea catalyzed proton transfer from hydrogen isocyanide to imine **32** to generate a catalyst-bound diastereomeric iminium/cyanide ion pair. Thereby, hydrogen isocyanide, as the tautomeric form of HCN, is stabilized by the thiourea moiety of **33**. The stabilization degree of the formed iminium ion by the catalyst is seen as the basis for enantioselectivity. Subsequent collapse of the ion pair and bond formation between the electrophile and the cyanide ion forms the α-amino nitrile. It should be emphasized that the productive catalytic cycle with **33** does not involve a direct imine–urea binding, although this interaction was observed both kinetically and spectroscopically in the Strecker reaction catalyzed by **25** (see above) [19].

Bifunctional catalysts bearing both an acidic and a basic/nucleophilic functionality are interesting for asymmetric organocatalysis. The catalysts **39** and **40** consist of a basic pyridine and a thiourea moiety that is intended to attract the imine species **38** with hydrogen bonds (Scheme 30.9) [23]. Despite catalyst loadings of 10 mol%, low conversion rates (17–25%) and poor ee values of 12–14% were observed. It was found by X-ray analysis that an analogous structure of **39** and **40** built intramolecular hydrogen-bonds between the thiourea- and pyridine-moiety, which prevented a tight imine–catalyst complex.



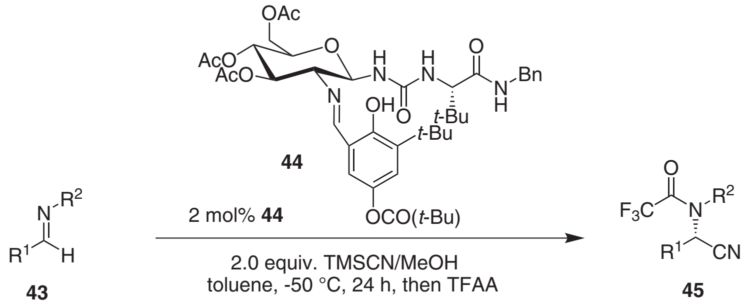
Scheme 30.9 Strecker reaction supported by pyridinyl-catalysts **39** and **40**.

Taking these observation into account and the fact that imidazole alone was a good promoter, the imidazole-based thiourea catalyst **42** was synthesized (Scheme 30.10) [24]. Higher ee's, up to 68% ee, had to be paid for with low conversion rates and vice versa.



Scheme 30.10 Imidazolyl-catalyst **42** as an improved bifunctional catalyst.

Inspired by the work of Jacobsen, Kunz and coworkers came up with catalyst **44**, a D-glucosamine derived analog of **25**, where the 1,2-*trans*-diaminocyclohexane is replaced with the a glucosamine unit (Scheme 30.11) [25]. Glucosaminylurea **44**, accessible in nine steps, proved to be an effective catalyst for the asymmetric Strecker reaction of *N*-allyl-protected aromatic aldimines **43**. Aliphatic and heteroaryl aldimines, as well as keto-imines, reacted only with moderate enantioselectivity. By reaction of an analogous structure of **44**, bearing a reversal arrangement of Schiff-base and thiourea-moiety in the sugar ring, it could be proved that the carbohydrate backbone is not just a cyclohexane surrogate but has an inherent influence on the obtained enantioselectivities.



R^1 = aryl; R^2 = allyl; 67-98% yield; 66-84%*ee* R^1 = 2-furyl; R^2 = allyl; 87% yield; 50%*ee*

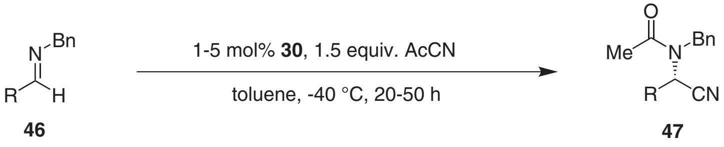
R^1 = *c*-hexyl; R^2 = benzyl; 60% yield; 47%*ee* 6,7-dimethoxyisoquinoline; 97% yield; 89%*ee*

Scheme 30.11 Imine-hydrocyanation using urea-catalyst **44** derived from D-glucosamine.

Building upon an early observation that α-oxonitriles readily react with imines to form the corresponding *N*-acylamino nitriles [26–28], List devised an asymmetric organocatalyzed acetylcyanation variant (Table 30.5) [29, 30]. Acetyl cyanide is commercially available and, as a liquid, is convenient to use. In addition, the use of acetyl cyanide makes further derivatization of the hydrocyanation compounds with, for example, TFAA obsolete. Using catalyst **30**, the reaction gave high enantioselectivities and high yields with aromatic, aliphatic, heteroaromatic, aliphatic-branched and -unbranched, and unsaturated imines.

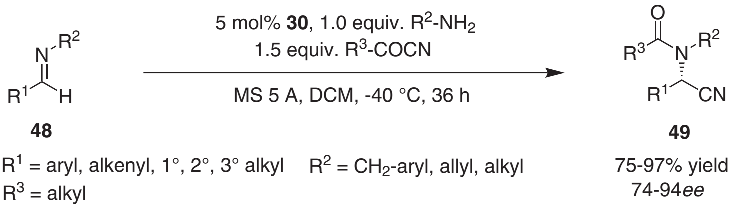
List and coworkers implemented the imine-forming step in a three-component Strecker reaction using Jacobsen's catalyst **30** (Scheme 30.12) [31]. In this way, different amines, acyl cyanides, and aldehydes were allowed to react with catalyst

Table 30.5 Asymmetric acyl-Strecker reaction supported by thiourea **30**.



Entry	R	Catalyst (mol%)	Yield (%)	ee (%)
1	Ph	1	94	96
2	4-Cl-Ph	1	87	98
3	4-MeO-Ph	1	95	96
4	2-Furyl	5	94	89
5	(*E*)-2-Ph-ethenyl	1	83	94
6	*n*-Bu	5	76	94
7	*c*-Hex	1	88	92
8	*t*-Bu	5	62	96

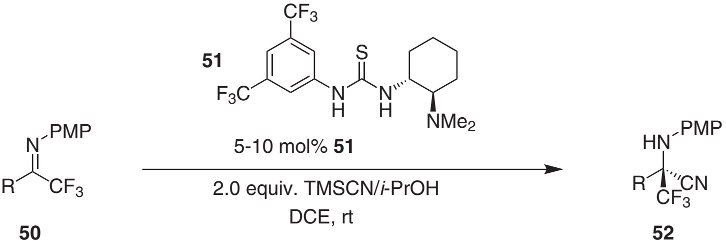
30 in the presence of molecular sieves to bind the reaction water resulting from imine condensation.


5 mol% 30, 1.0 equiv. R2-NH2
1.5 equiv. R3-COCN
MS 5 A, DCM, -40 °C, 36 h
48
49
R1 = aryl, alkenyl, 1°, 2°, 3° alkyl R2 = CH2-aryl, allyl, alkyl
R3 = alkyl
75-97% yield
74-94ee

Scheme 30.12 Three-component acyl-Strecker reaction catalyzed by thiourea **30**.

Quaternary amino acids bearing a trifluorinated methyl group in the α-position are of particular interest due to their special physicochemical properties. In 2010, Enders and coworkers showed that trifluoromethyl substituted keto-imines **50** were excellent substrates for the synthesis of α-trifluoromethyl amino nitriles via a thiourea-catalyzed Strecker reaction (Table 30.6) [32]. Despite long reaction times (>5 d) the hydrocyanation proceeded, in general, smoothly at room temperature in good yields with high selectivities by using TMSCN/*i*-PrOH and 5 mol% of Takemoto's catalyst **51**. Aryl keto-imines **50** were very good substrates independent of the electronic nature of their substituent (entries 1, 3) but substitutions at the

Table 30.6 Asymmetric acyl-Strecker reaction supported by thiourea **51**.



Entry	R	Catalyst (mol%)	Time (d)	Yield (%)	ee (%)[a]
1	Ph	5	5	90	95 (>99)
2	2-MeO-Ph	10	27[b]	25[b]	88
3	4-Br-Ph	5	6	99	91
4	2-Furyl	10	17	66	92
5	(*E*)-2-Ph-ethenyl	10	27	51	93
6	*n*-Pent	10	17	82	89
7	*i*-Pr	10	22	50	85

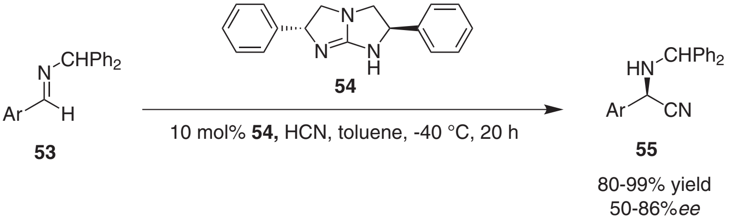
a) Value in parenthesis indicates the ee after recrystallization.

b) Reaction aborted, 96% yield based on recovered starting material.

ortho-position (entry 2) proved problematic. In cases of heteroaromatic imines (entry 4), alkenyl imines (entry 5), and aliphatic imines (entries 6, 7), higher catalyst loadings of **51** (10 mol%) and longer reactions times (>17 d) were required to obtain generally good enantioselectivities with moderate to high yields. Although the reaction was intolerant to changing the N-protecting group, PMP (*para*-methoxyphenyl) was readily removable from **52** with periodic acid. A similar approach was pursued by the Zhou group. In their studies the effect of fluorine on the selectivity and the reactivity was observed and discussed [33].

30.7
Guanidines as Catalysts for the Strecker Reaction

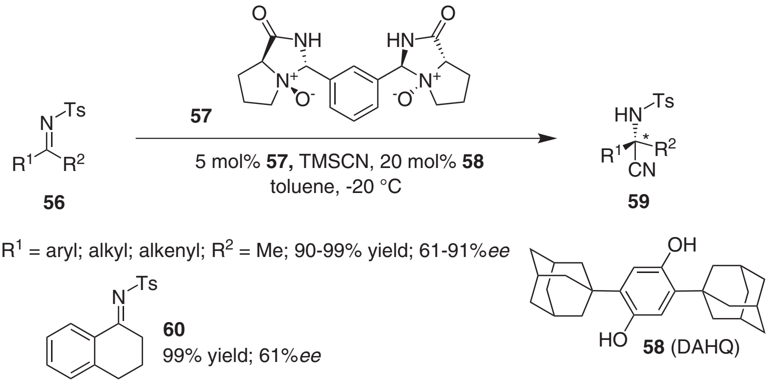
In 1999, Corey and coworker came up with the bifunctional C_2-symmetric guanidine **54** (Scheme 30.13) [34]. Using *N*-benzhydryl protected aryl aldimines **53**, the corresponding (*R*)-Strecker adducts **55** were obtained in high yields (80–99%) and in moderate to good enantioselectivities (50–86% ee). Liquid HCN was used as cyanide source, which is a disadvantage for safety reasons. Regarding the mechanism, HCN presumably protonates the catalyst **54** and subsequently the so-protonated guanidinium–cyanide complex assembles with the aldimine via hydrogen bonds. The crucial effect of the benzhydryl group of **53** in reaching high enantioselectivities might be explained by π-stacking as attractive interactions between **53** with the catalyst. Interestingly, aliphatic substrates showed an inverse sense of stereoinduction and, thus, (*S*)-Strecker were formed in moderate ee's. Catalyst **54** proved to be recoverable from the crude reaction mixture and could be prepared in nine steps in 24% overall yield from methyl (*R*)-phenylglycinate.



Scheme 30.13 Asymmetric hydrocyanation supported by a chiral bicyclic guanidine.

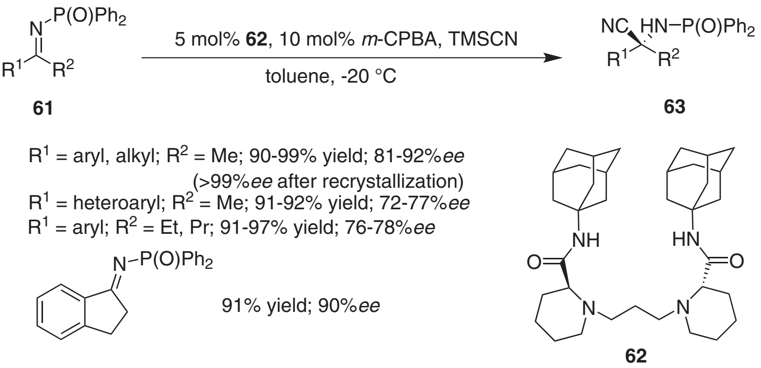
30.8
N,N′-Dioxides and Bis-Formamides as Catalysts for the Strecker Reaction

In 2001, axial chiral *N,N′*-dioxides were introduced as promoters for the asymmetric Strecker reaction of aldimines. However, stoichiometric quantities of catalyst had to be used [35], affording adducts of aryl and alkenyl aldimines in modest to good enantioselectivities (49–95% ee, 99% ee after recrystallization) with good yields (up to 96%) [36]. By changing the catalyst structure from a C_2-symmetrical constitution to an aryl-linked bis-L-prolinamide structure, catalyst **57** afforded on average good results in sub-stoichiometric quantities for the asymmetric hydrocyanation of methyl keto-imines **56** and **60** (Scheme 30.14) [37]. Besides catalyst **57**, DAQH [2,5-di-(1-adamantyl)hydroquinone] (**58**) as a sterically demanding hydroquinone additive was necessary to obtain high enantioselectivities. Although alcoholic additives are known to react with TMSCN to generate HCN, the system was inert to HCN addition, which led to speculation that a hypervalent silicate species was present. Here, TMSCN is fixed and activated by the twin *N,N′*-dioxides from **57** to produce a hypervalent silicate; meanwhile the imine **56** is recognized by the catalyst with hydrogen bonds.


57
5 mol% 57, TMSCN, 20 mol% 58
toluene, -20 °C
56
59
R1 = aryl; alkyl; alkenyl; R2 = Me; 90-99% yield; 61-91%ee
60
99% yield; 61%ee
58 (DAHQ)

Scheme 30.14 Catalysis by aryl linked *N,N′*-dioxides derived from L-prolinamide.

By application of the *in situ* formed bis-L-peridinamide-derived *N,N′*-dioxide catalyst to *N*-diphenylphosphinoyl keto-imines **61**, generally higher ee's for aryl, aliphatic, and cyclic substrates were reached in comparison to catalyst **57** (Scheme 30.15) [38]. The reaction could also be extended to ethyl or propyl substituted aryl keto-imines **61** with good to high ee's and high yields. Besides *m*-CPBA addition, promoting the oxidation of **62** to the catalytic active *N,N′*-dioxide, no further additive was necessary, which led, as mentioned before, to the conclusion that TMSCN is the reacting species and not *in situ* generated HCN. In addition, it was observed that both *N*-oxide functionalities were needed for high ee's, indicating that TMSCN is activated by both N–O donors to form a possible hypervalent silicate. The catalyst could be readily synthesized and the reaction tolerated moisture well, but the long reaction times (>60 h) were a handicap.



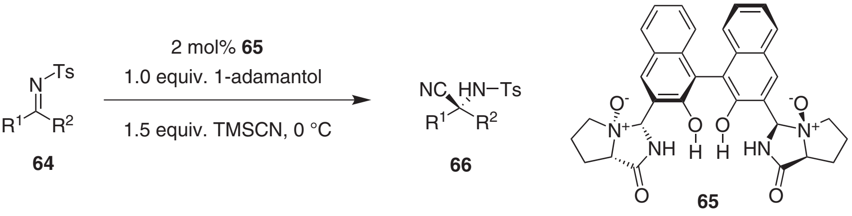
R^1 = aryl, alkyl; R^2 = Me; 90-99% yield; 81-92%*ee* (>99%*ee* after recrystallization)
R^1 = heteroaryl; R^2 = Me; 91-92% yield; 72-77%*ee*
R^1 = aryl; R^2 = Et, Pr; 91-97% yield; 76-78%*ee*
91% yield; 90%*ee*

Scheme 30.15 Strecker reaction of phosphinoyl ketimines by an *in situ* prepared catalyst.

By replacing the linker in previously used *N,N′*-dioxides with a rigid axial chiral (*S*)-BINOL-derived backbone, high yields and enantioselectivities were obtained from aryl (entries 1, 2), heteroaryl (entry 3), aliphatic (entry 4), and alkenyl (entry 5) methyl keto-imines **64** by use of just 2 mol% **65** (Table 30.7) [39]. In addition, the use of cyclic keto-imine **60** (entry 6) as well as ethyl, propyl (entry 7), and phenyl substituted aryl keto-imines (entry 8) as substrates were possible, yielding products **66** in high to excellent enantiopurities. Despite convenient reaction conditions, the reaction times were lengthy (>72 h).

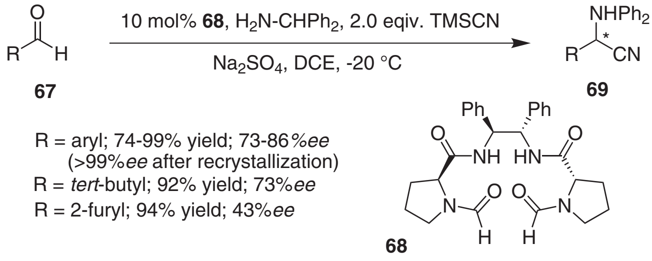
The concept of connecting two L-prolinamides portions over a chiral backbone structure was applied on the C_2-symmetrical bis-formamide catalyst **68** for the

Table 30.7 Hydrocyanation of ketimines using (*S*)-BINOL-derived *N,N′*-dioxide **65**.



Entry	R^1	R^2	Time (h)	Yield (%)	ee (%)
1	Ph	Me	72	93	97
2	4-MeO-Ph	Me	120	80	99
3	2-Furyl	Me	72	88	95
4	*t*-Bu	Me	72	96	93
5	(*E*)-2-Ph-ethenyl	Me	72	86	95
6	**60**		120	73	98 (*R*)
7	Ph	*n*-Pr	120	74	95
8	2-Cl-Ph	Ph	120	76	90

three-component Strecker reaction of various aldehydes with (1,1-diphenyl)methylamine, TMSCN, and sodium sulfate (Scheme 30.16) [40]. The chiral DMF analog **68** provided in general good to high yields (74–99%) and moderate to high enantiopurities (43–84% ee, >99% ee after recrystallization) with aryl aldehydes **67** as well as furfural and *tert*-butyl aldehyde.

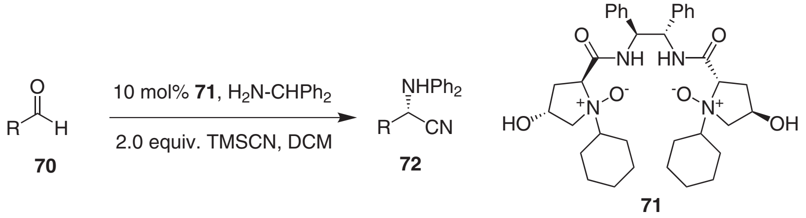

10 mol% **68**, H$_2$N-CHPh$_2$, 2.0 eqiv. TMSCN
Na$_2$SO$_4$, DCE, -20 °C
67
69
68

R = aryl; 74-99% yield; 73-86%*ee* (>99%*ee* after recrystallization)
R = *tert*-butyl; 92% yield; 73%*ee*
R = 2-furyl; 94% yield; 43%*ee*

Scheme 30.16 Chiral bis-formamides as catalysts for the three-component Strecker reaction.

The same group achieved further improvements in the three-component Strecker reaction by applying the *trans*-4-hydroxy-L-prolinamide derived *N,N′*-dioxide catalyst **71** (Table 30.8) [41]. In general, high yields and good to high enantioselectivities were obtained by the reaction of aryl (entries 1–3), α,β-unsaturated (entry 5), α-unbranched (entry 6), and α-branched (entry 7) aldehydes **70** with (1,1-diphenyl)methylamine and TMSCN. Poor stereoinduction was

Table 30.8 Three-component Strecker reaction supported by a *N,N′*-dioxide.



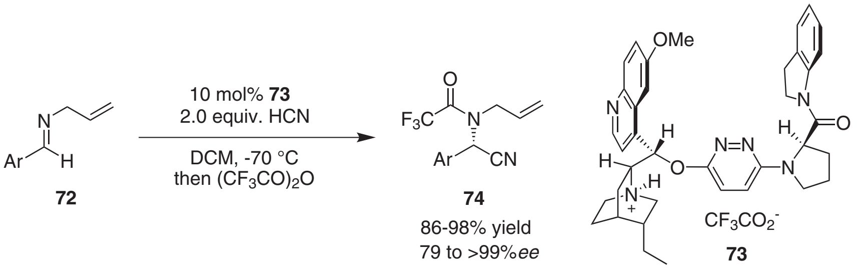
Entry	R	Temp. (°C)	Time (h)	Yield (%)	ee (%)[a]
1	Ph	−45	36	93	90 (99)
2	2-NO$_2$-Ph	−20	80	68	81
3	4-Me-Ph	−40	36	98	80 (99)
4	2-Furyl	Not reported	Not reported	Not reported	48
5	(*E*)-*n*-pent-1-enyl	−40	40	87	72
6	*n*-Pent	−40	30	96	81
7	*c*-Hexyl	−40	32	99	84

a) Value in parenthesis indicates the ee after recrystallization.

observed on using the heteroaryl aldehyde furfural (entry 4) and the reactions suffered from long reaction times (>30 h). No further addition of a drying agent was needed and experiments with a preformed imine were not as satisfying as those with *in situ* generated imines, indicating that water played a crucial role for the catalysis.

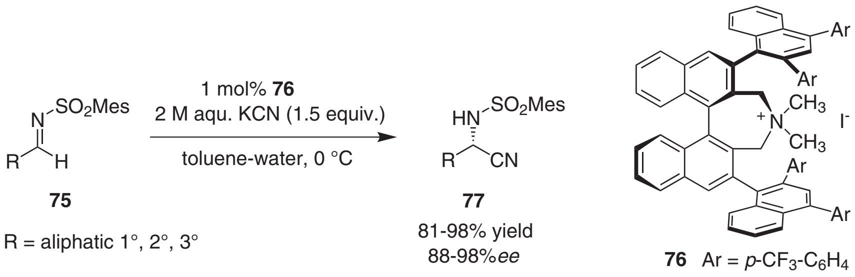
30.9
Chiral Quaternary Ammonium Salts as Catalysts for the Strecker Reaction

In 2004, Corey used the chiral ammonium salt **73** for the enantioselective Strecker reaction of *N*-allyl protected aryl aldimines **72** (Scheme 30.17) [42]. Various *N*-allyl protected aryl aldimines **72** underwent the reaction with 10 mol% **73** by using free HCN to furnish α-amino nitriles **74** in high yields (86–98%) and good to excellent enantioselectivities (79 to >99%ee). The logic behind application of the U-shaped catalyst is that the protonated quinuclidine moiety of **73** activates the imine part of the substrate **72** by hydrogen bonding in the pre-transition state. The aryl substituent of the aldimine **72** seems to interact with the postulated binding pocket of catalyst **73**. This proposed binding model is consistent with the observed poor enantioselectivities for aliphatic substrates. Owing to the lower steric demand in the assembly with catalyst **73**, the *N*-allyl protected imines were superior substrates. Although high enantiopurities were reached and catalyst **73** was readily accessible from dihydroquinidine (three steps with 68% overall yield), the use of liquid HCN and the limited substrate scope were drawbacks.



Scheme 30.17 Strecker reaction supported by chiral ammonium salt **73**.

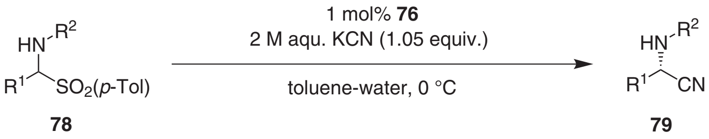
In 2006, Ooi conducted an asymmetric Strecker reaction under phase-transfer conditions (PTC) employing a chiral quaternary ammonium salt **76** with a tetranaphthyl backbone (Scheme 30.18) [43]. Under biphasic conditions, aqueous KCN could be used as an inexpensive and safe surrogate for HCN. With 1 mol% of catalyst **76** the reaction in toluene–water at 0 °C proceeded smoothly in relatively short reaction times (2–8 h). In doing so, α-branched and α-unbranched aliphatic *N*-mesitylenesulfonyl imines **75** were transformed in high yields and good to high enantioselectivities into the corresponding adducts **77**, but these conditions were not applicable to aromatic substrates. An X-ray analysis confirmed that the tetranaphthyl-backbone forms a chiral aromatic cavity around the quaternary ammonium ion. In addition to endowing enantiocontrol, the catalysts role is to extract sufficiently the cyanide anion as an ammonium cyanide with enhanced nucleophilicity.



Scheme 30.18 Asymmetric Strecker reaction with **76** under phase-transfer conditions.

Using α-unbranched aldimines for the asymmetric Strecker reaction under PTC, somewhat lower ee's and yields were obtained than with branched analogues. These results can be ascribed to the partial imine hydrolysis and uncatalyzed cyanation of primary and secondary aldimines under PTC [44]. Therefore, *N*-arylsulfonyl α-amido sulfones **78** were employed for *in situ* generation of the imines species (Table 30.9). With catalyst **76**, generally higher yields and higher enantioselectivities were obtained for various primary and secondary aliphatic *N*-arylsulfonyl α-amido sulfones **78**.

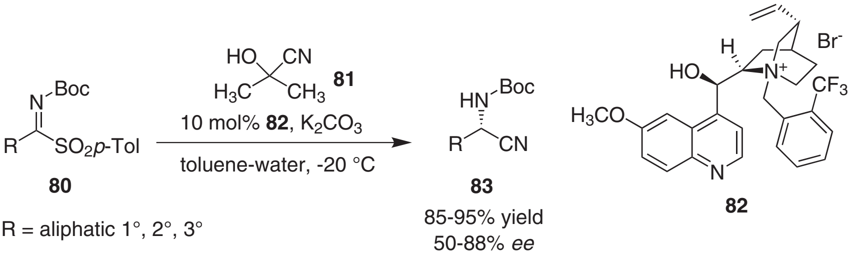
Table 30.9 Asymmetric Strecker reaction under biphasic conditions.



Entry	R^1	$R^{2a)}$	Time (h)	Yield (%)	ee (%)
1	*c*-Oct	Mts	2	99	98
2	*i*-Pr	Mts	1.5	99	97
3	*n*-Hept	Mts	1	96	84
4	$(CH_3)_2CHCH_2$	Mtr	1	99	93
5	$PhCH_2$	Mtr	1	86	86

a) Mts = mesitylenesulfonyl (2,4,6-trimethylphenylsulfonyl);
Mtr = 4-methoxy-2,3,6-trimethylphenylsulfonyl.

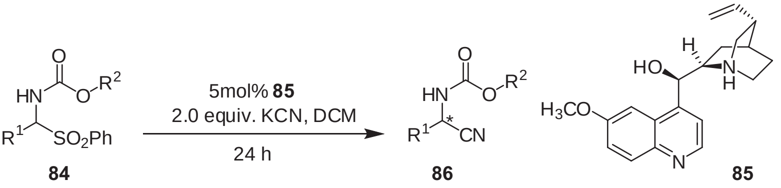
A similar concept of was pursued by the Ricci group [45]. The hydrocyanation of aliphatic *N*-Boc α-amido sulfones **80** was accomplished with the cinchona-derived quaternary ammonium salt **82** (Scheme 30.19). Here, acetone cyanohydrin **81** was employed as cyanide source that is cheap, has good solubility in organic solvents, and is available on a large scale. (*S*)-Configurated primary, secondary, and tertiary aliphatic *N*-Boc α-amino nitriles **83** were obtained in high yields (85–95%), but enantioselectivities were lower (50–88% ee) in comparison to Ooi's protocol [43, 44].



Scheme 30.19 Hydrocyanation of α-amido sulfones **80** under phase transfer conditions.

Bräse and coworkers finally accomplished transformation of the aromatic counterparts of **84** into the α-amino nitriles **86**, by using the naturally occurring alkaloid quinine **85** (Table 30.10) [46]. Solid KCN led to liberation of the free *N*-carbamoyl imine by deprotonation of the α-amido sulfone **84** and subsequent elimination of the sulfinate. The so-generated HCN could subsequently protonate the catalyst **85**

Table 30.10 Asymmetric Strecker reaction using natural occurring alkaloid **85**.



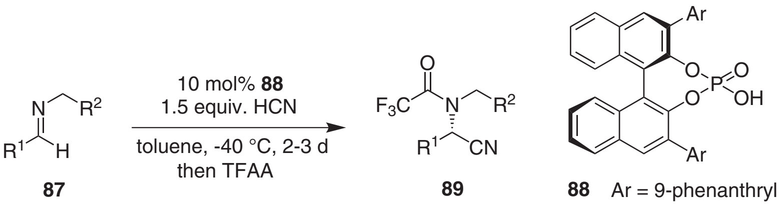
Entry	R^1	R^2	Temperature (°C)	Yield (%)	ee (%)
1	Ph	*t*-Bu	–10	82	57 (*R*)
2	3-Me-Ph	*t*-Bu	–10	99	74 (*R*)
3	1-Naphthyl	*t*-Bu	–10	95	79 (*R*)
4	Ph	$C(Me)_2$(*i*-Pr)	–10	95	56 (*R*)
5	Ph	$C(Me)_2$(Bn)	0	53	64 (*S*)
6	3-Cl-Ph	*t*-Bu	–10	80	34 (*S*)

and strong evidence is given that the enantio-discriminating step involves an intermediately formed *N*-protonated quinidinium ion. Although water was well-tolerated by the catalyst, an absence of water seemed crucial to prevent hydrolysis of the intermediately generated aromatic imines. In general, various substituted aryl *N*-Boc α-amido sulfones **84** were transformed into their corresponding nitriles in high yields (80–99%) and in moderate to good enantioselectivities (57–79% ee) (entries 1–3), but ee values dropped for adducts from electron-poor aromatic imine precursors (entry 6; 34–48% ee). Variation at the carbamoyl group was also tolerated (entries 4, 5), but without any clear structure–selectivity relationship. Interestingly, the sense of stereoinduction [(*R*) or (*S*)] was inconsistent.

30.10
BINOL-Phosphates as Catalysts for the Strecker Reaction

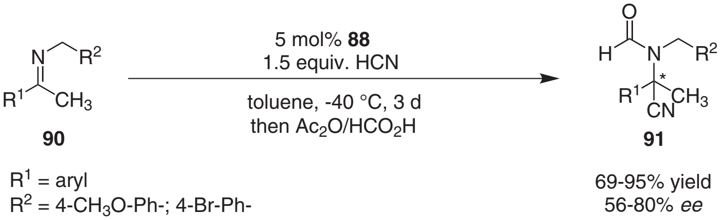
Rüping and coworkers extended the group of organocatalysts by successful employment of BINOL-phosphate **88** (Table 30.11) [47]. It was reasoned that imine **87** was activated by catalytic protonation with **88**. Subsequent addition of hydrogen cyanide to the iminium ion, present as a chiral ion pair with the conjugated base of **88**, succeeded in yielding the Strecker adduct **89**. The reaction of various aryl (entries 1, 2, 4, 5) and heteroaryl imines **87** (entry 3), bearing either electron-withdrawing or electron-donating groups, proceeded smoothly and the trifluoroacetylated adducts were obtained in good to high yields (53–97%) and in generally high ee's (85–99% ee). When aliphatic imines were employed, enantioselectivities decreased and long reaction times (48–72 h) were necessary.

Table 30.11 Hydrocyanation of imines catalyzed by Brønsted acid **88**.



Entry	R¹	R²	Yield (%)	ee (%)
1	4-CF_3-Ph	4-MeO-Ph	53	96
2	1-Naphthyl	Ph	85	99
3	2-Thienyl	Ph	77	95
4	4-MeO-Ph	Ph	97	93
5	4-Cl-Ph	Ph	69	85

The scope of the Brønsted acidic catalyst **88** could be extended to the hydrocyanation of aromatic methyl keto-imines **90**, but enantioselectivities of the formylated Strecker adducts **91** were in general lower (56–80% ee) but with good to high yields (69–95%) (Scheme 30.20) [48].

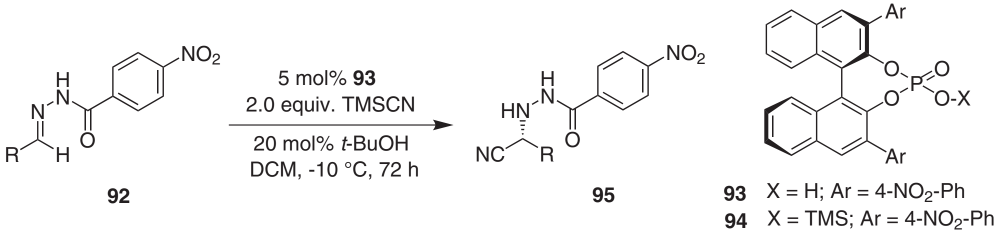


Scheme 30.20 Brønsted acid catalyzed Strecker reaction of keto-imines.

The BINOL phosphate catalyzed cyanide addition was also examined as a three-component-Strecker reaction of an acetophenone derivative with an aniline component; only poor stereoselectivities (20–40% ee) were obtained in reasonable yields (73–81%) [49].

The group of Tsogoeva discovered that BINOL-phosphate catalyst **93** can promote the enantioselective addition of TMSCN to aliphatic hydrazones **92** (Table 30.12) [50]. The so-formed α-hydrazino nitriles **95** can be readily transformed via acidic hydrolysis into biologically and synthetically important α-hydrazino acids. In general, *N*-*p*-NO$_2$-benzoyl-protected aliphatic hydrazones **92** could be converted in good enantioselectivities (71–93% ee). The yields showed inconsistency, but

Table 30.12 Hydrocyanation of imines catalyzed by Lewis acid **94**.



93 X = H; Ar = 4-NO$_2$-Ph
94 X = TMS; Ar = 4-NO$_2$-Ph

Entry	R	Yield (%)	ee (%)
1	$(CH_3)_2CHCH_2$	31	90
2	Me	54	71
3	Et	95	93
4	$Ph(CH_2)_2$	79	92
5	$CH_3S(CH_2)_2$	26	78

unbranched substrates reached higher yields (entry 2, 3) than β-branched (entry 1) or thioether-containing substrates (entry 5). Interestingly, experiments confirmed that the actual catalytic species is not a Brønsted acid but rather the Lewis acid **94**, generated *in situ* from the catalyst **93** and TMSCN.

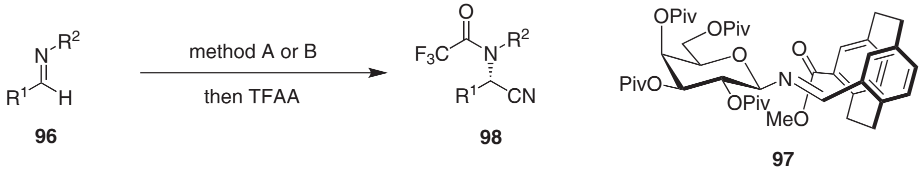
30.11
Other Catalysts for the Strecker Reaction

In 2007, Kunz presented a new class organocatalysts that consists of glycosyl amines and planar-chiral [2.2]paracyclophane derivatives [51]. Within this new class, *N*-galactosyl[2.2]paracyclophane carbaldimine **97** proved to be a valuable catalyst for the enantioselective Strecker reaction of aromatic (entries 1, 5) and aliphatic aldimines **96** (entries 2–4) (Table 30.13). Aromatic products were obtained in good yields (55–87%) and reasonable enantiopurities (71–82% ee), aliphatic substrates instead led to higher yields (84–89%) and better enantiopurities (88–99% ee).

For the catalytic mechanism of **97** it can be reasoned that a proton, derived from HCN, is trapped between the carbaldimine nitrogen and carbonyl oxygen from the pseudo-geminal ester group of **97** (Figure 30.1). The protonated catalyst can so coordinate the aldimine species to provide substrate activation and enantiodiscrimination.

Experiments showed that TADDOL (2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol) can also be applied to catalyze the asymmetric Strecker reaction of aromatic *N*-benzyl aldimines [48]. In initial experiments some asymmetric introduction (22–56% ee) was gained by moderate to high yields (68–93%).

Table 30.13 Imine hydrocyanation promoted by a sugar-derived catalyst.



method A: 2-5 mol% **97**, **96**, toluene, -78 °C to -50°C, then 2.0 equiv. TMSCN/MeOH, -50°C to -20°C
method B: 10 mol% **97**, 1.2 equiv. TMSCN/MeOH, toluene, -50°C, then **96**

Entry	R¹	R²	Method	Time (h)	Yield (%)	ee (%)
1	Ph	Allyl	A	20	55	71
2	*i*-Pr	Allyl	B	24	89	96
3	*c*-Hex	Bn	B	24	87	88
4	Isoamyl	Bn	B	24	84	99
5	4-MeO-Ph	Bn	B	24	87	82

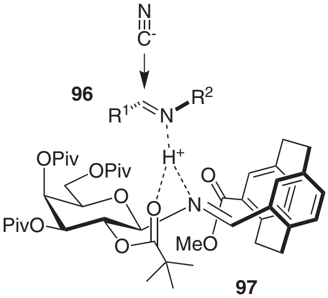


Figure 30.1 Activation of the aldimine substrate **96** by the *N*-galactosyl[2.2]paracyclophane carbaldimine catalyst **97**.

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31

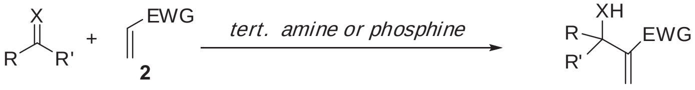
The Morita–Baylis–Hillman (MBH) and Hetero-MBH Reactions

Yin Wei and Min Shi

31.1
Introduction

Recent progress in organic chemistry has clearly established that the development of a reaction depends on two main criteria: atom economy and selectivity (chemo-, regio-, stereo-). Among the carbon–carbon bond-forming reactions, the Morita–Baylis–Hillman (MBH) reaction has become one of the most useful and popular carbon–carbon bond-forming reactions with enormous synthetic utility, promise, and potential. The origin of Morita–Baylis–Hillman reaction dates back to 1968 to a pioneering report presented by Morita (phosphine-catalyzed reaction) [1] and then Baylis and Hillman described a similar amine catalyzed reaction in 1972 [2]. Though this reaction is promising and fascinating it was, unfortunately, ignored by organic chemists for almost a decade after its discovery. However, at the beginning of the 1980s organic chemists such as Drewes, Hoffmann, Perlmutter, and Basavaiah started looking at and exploring various aspects of this important reaction [3]. Especially since the mid-1990s, particularly in the last decade, this reaction and its applications have received remarkable growing interest, and the exponential growth of this reaction and its importance are evidenced by numerous research papers.

The MBH reaction can be broadly defined as a condensation of an electron-deficient alkene and an aldehyde catalyzed by tertiary amine or phosphine. Instead of aldehydes, imines can also participate in the reaction if they are appropriately activated, and in this case the process is commonly referred to as the aza-Morita–Baylis–Hillman (aza-MBH) reaction (Scheme 31.1). These operationally



R = aryl, alkyl, heteroaryl, *etc.*; R' = H, CO_2R'', alkyl, *etc.*
X = O, NCO_2R'', NSO_2Ar, *etc.*
EWG = COR'', CHO, CN, CO_2R'', $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh, *etc.*

Scheme 31.1

Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, First Edition.
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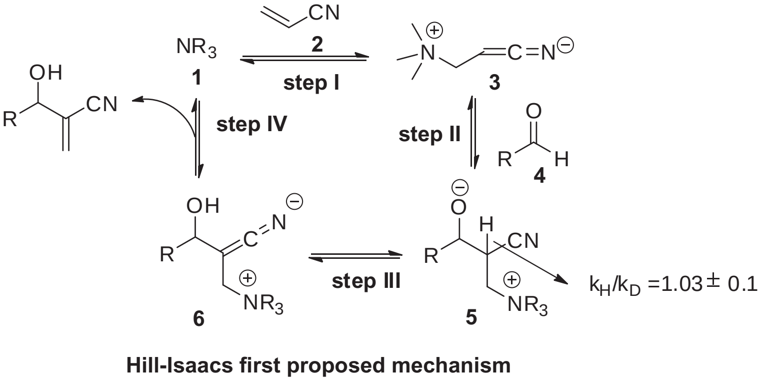
simple and atom-economic reactions afford α-methylene-β-hydroxy-carbonyl or α-methylene-β-amino-carbonyl derivatives, which consist of a contiguous assembely of three different functionalities.

Interest in the MBH/aza-MBH reaction and its applications in synthesis has been growing and many research groups have initiated work on different facets of this reaction since 1990s. In recent years, several major reviews [4] and mini reviews [5] regarding the development of this reaction and its applications have been published. Since Basavaiah's major review on the MBH/aza-MBH reaction was published in 2010 [4e], covering advances made before the end of 2008, numerous studies have been made. This chapter mainly focuses on advances of MBH/aza-MBH reactions and the asymmetric versions from 2009 to 2011. We hope that this chapter will satisfy the expectations of readers interested in the development of the field and looking for up-to-date information on the MBH/aza-MBH reaction.

31.2
Recent Mechanistic Insights into the MBH/aza-MBH Reaction and Its Asymmetric Version

31.2.1
Amine Catalyzed Mechanism

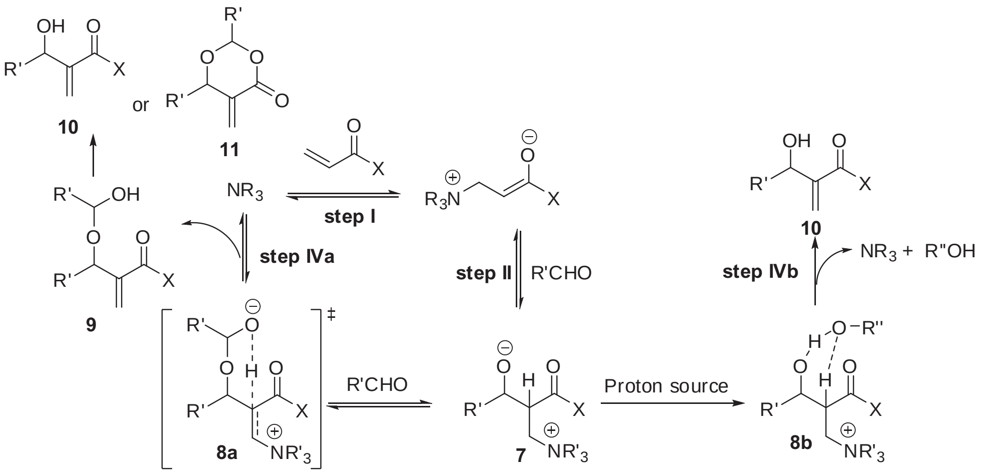
Although the elementary steps of the MBH reaction have been described in the earliest publications [1a], the exact reaction mechanism, in particular that controlling the asymmetric induction, has been debated frequently, and remains as the core of the mechanistic discussion. The commonly accepted mechanism for the MBH reaction was first proposed by Hoffmann [3b] and refined from kinetic studies by Hill and Isaacs [6] in the late 1980s and others [7]. Their proposed



Scheme 31.2

mechanism is described in Scheme 31.2. The first reaction step I involves 1,4-addition of the catalytic tertiary amine **1** to the activated alkene **2** (α,β-unsaturated carbonyl compounds, nitriles, etc.) to generate the zwitterionic amine-acrylate **3**. In step II, **3** forms intermediate **5** by adding to aldehyde **4** via an aldolic addition reaction. Step III involves an intramolecular proton shift within **5** to form **6**, which subsequently generates the final MBH adduct and releases the catalyst **1** via an *E*2 or *E*1cb elimination in step IV. Owing to the low kinetic isotopic effect (KIE = 1.03 ± 0.1, using acrylonitrile as electron-deficient alkene and acetaldehyde as carbon nucleophile for the MBH reaction) measured by Hill and Isaacs and the dipole increase by charge separation, step II was initially considered as the MBH rate-determining step (RDS, Scheme 31.2). This suggested mechanism was supported by subsequent independent investigations, including isolation of one intermediate in the catalytic cycle that was confirmed by X-ray analysis [8] and the interception of all key intermediates using electrospray ionization with mass and tandem mass spectrometry [9].

More recently, McQuade *et al.* [10] and Aggarwal *et al.* [11] re-evaluated the MBH mechanism using kinetics and theoretical studies, focusing on the proton-transfer step. According to McQuade, the MBH reaction is second order relative to the aldehyde and shows a significant kinetic isotopic effect (KIE: $k_H/k_D = 5.2 \pm 0.6$ in DMSO). Interestingly, regardless of the solvent (DMF, MeCN, THF, $CHCl_3$), the KIEs were found to be greater than 2, indicating the relevance of proton abstraction in the rate-determining step. Based on these new data, McQuade *et al.* proposed a new mechanism for the proton-transfer step (Scheme 31.3),



McQuade proposal
proton-transfer step via a six-membered TS
formed with a second molecule of aldehyde

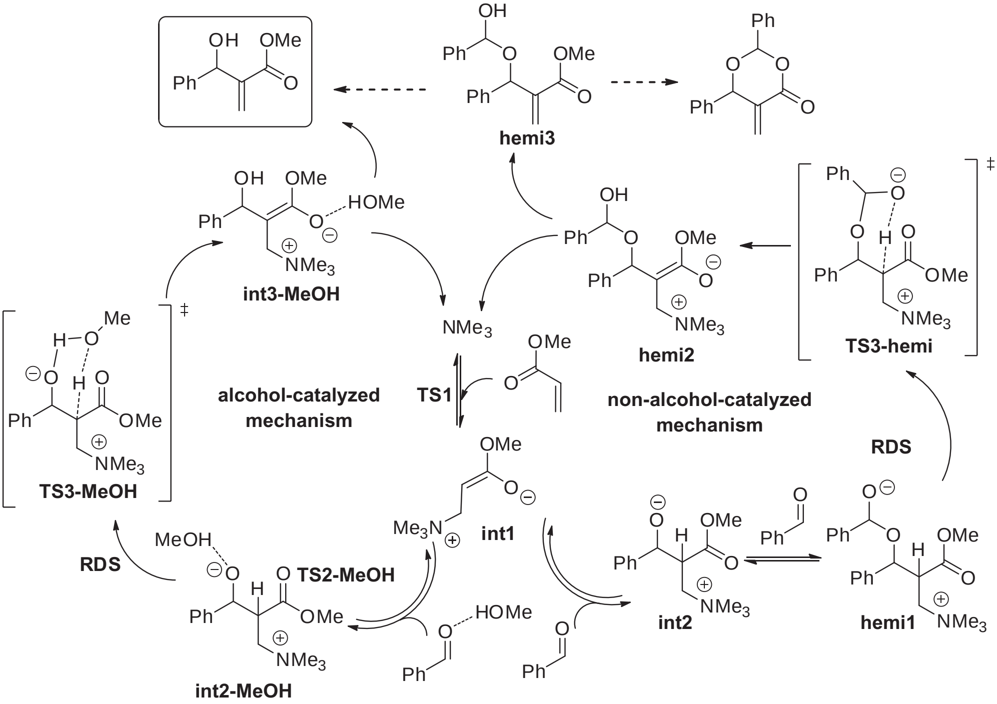
Aggarwal proposal
proton-transfer step via a six-membered
intermediate formed by autocatalysis

Scheme 31.3

suggesting the proton transfer step as the RDS. Soon after this, based on their kinetic studies, Aggarwal also proposed that the proton transfer step is the rate-determining step but only at the beginning (≤20% of conversion), then step II becomes the RDS when the product concentration builds up and proton transfer becomes increasingly efficient. Apparently, the MBH adducts **10** may act as a proton donor and therefore can assist the proton-transfer step via a six membered intermediate (Scheme 31.3). This model also explains the autocatalytic effect of the product. More recently, Eberlin and Coelho performed complementary investigations on the MBH reaction mechanism via ESI-MS(/MS) [12]. New key intermediates for the RDS of the MBH reaction have been successfully intercepted and structurally characterized, providing strong experimental evidence that the mechanisms proposed by McQuade *et al.* and Aggarwal *et al.* are both possible.

Besides kinetic studies, theoretical studies on the MBH mechanism were conducted initially by Xu [13] and Sunoj [14]. Subsequently, Aggarwal performed an extensive theoretical study, which supported their own kinetic observations and those of McQuade about the proton transfer step [15]. They proposed that the proton-transfer step can proceed via two pathways: (i) addition of a second molecule of aldehyde to form a hemiacetal alkoxide (hemi1) followed by rate-limiting proton transfer as proposed by McQuade (non-alcohol-catalyzed pathway) and (ii) an alcohol acts as a shuttle to transfer a proton from the α-position to the alkoxide of int2 (Scheme 31.4). In addition, a few computational studies have appeared recently in the literature that attempt to address mechanistic questions in the MBH reaction, including the addition of explicit water or methanol molecules [16]. However, in all these studies the inappropriate B3LYP method was used, or potential electronic energies were employed to describe the energetics instead of the more adequate free energies. Notably, the theoretical approach of Sunoj [14, 17], who employed CBS-4M and mPW1K methods to compute the free energy barriers for the reaction, is interesting but only compares the energetics of the direct proton transfer pathways (via a four-membered transition structure) and the proton 1,3-shift assisted by water, omitting the possibility of assistance by a second molecule of aldehyde or other protic species. More recently, Cantillo and Kappe presented a detailed computational and experimental reinvestigation on the amine-catalyzed MBH reaction of benzaldehyde with methyl acrylate [18]. They demonstrated that increasing temperature results in a switching of the thermodynamic equilibrium from exergonic to endergonic at even moderate temperature levels – which explains why it is impossible to accelerate this synthetically valuable transformation by increasing the reaction temperature – through variable-temperature experiments and MP2 theoretical calculations of the reaction thermodynamics. The complex reaction mechanism for the MBH reaction was investigated through an in-depth analysis of the suggested alternative pathways, using the M06-2X computational method. The results provided by this theoretical approach are in agreement with all the experimental/kinetic evidence such as reaction order, acceleration by protic species (methanol, phenol), and autocatalysis. Depending on the specific reaction conditions both suggested pathways (Aggarwal and

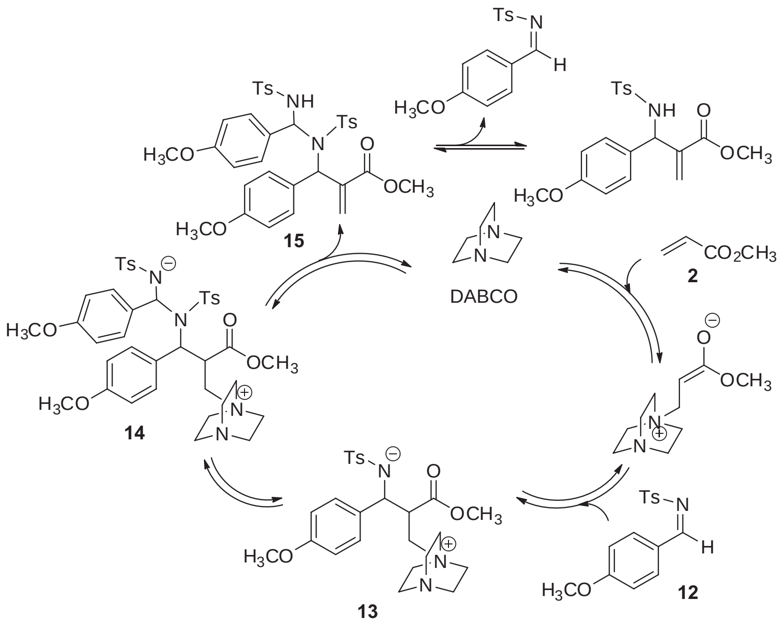
McQuade pathways) are competing mechanisms, and depending on the amount of protic species and the reaction progress (early or late stage) either of the two mechanisms is favored.



Scheme 31.4

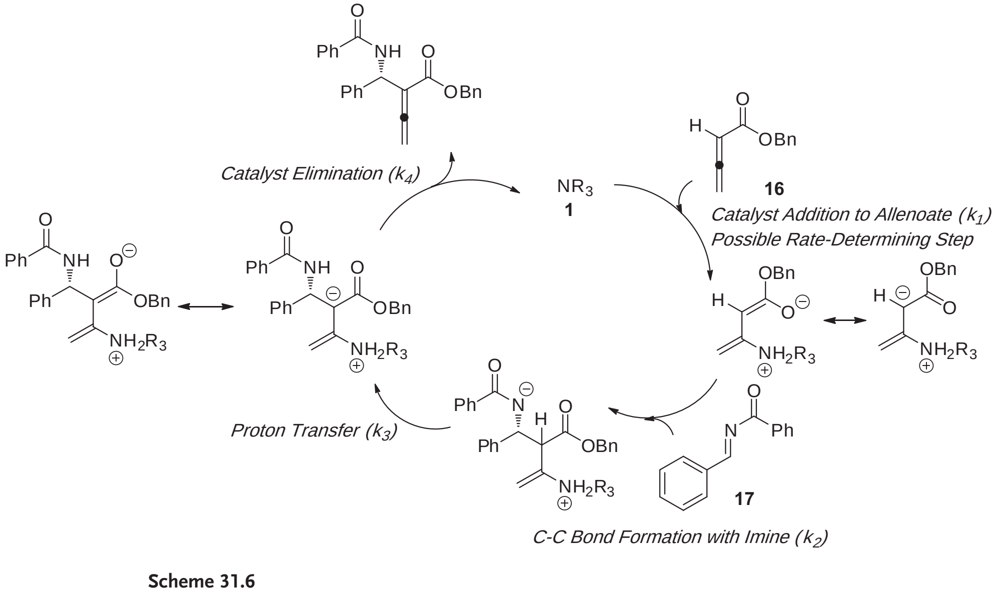
Recently, Eberlin and Coelho have investigated the mechanism of the aza-MBH reaction via ESI-MS(/MS) spectrometry and proposed a rational mechanism [19]. They monitored the DABCO-catalyzed aza-MBH reaction of methyl acrylate **2** (R = CO_2CH_3) with imine **12** by ESI-MS(/MS) spectrometry and intercepted the key intermediates **13** and **15** and also a unique bis-sulfonamide intermediate **14.** Based on their results, they proposed the mechanistic cycle for the aza-MBH reaction depicted in Scheme 31.5.

Miller and coworkers have performed kinetic studies on a pyridylalanine-peptide catalyzed enantioselective coupling of allenoates **16** and *N*-acyl imines **17** to investigate the mechanism of the aza-MBH reaction [20]. In the catalytic cycle of a typical MBH/aza-MBH reaction, the proton transfer step or C–C bond formation is often considered as the rate-determining step. However, through mechanistic



Scheme 31.5

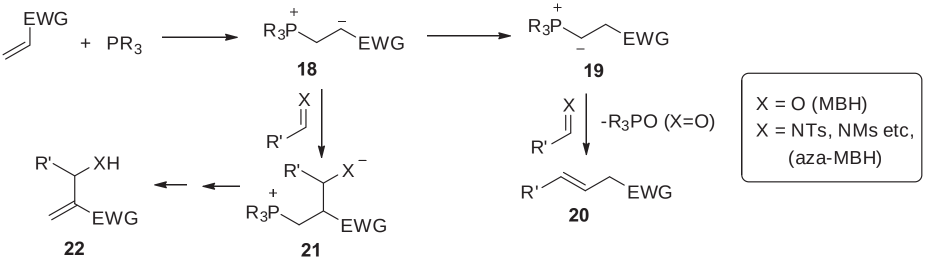
experiments, including kinetics and hydrogen/deuterium KIEs, the authors determined that the allenoate aza-MBH follows a divergent mechanism in comparison to typical MBH/aza-MBH reactions. In this pyridylalanine-peptide catalyzed aza-MBH reaction, catalyst addition becomes the rate-determining step (Scheme 31.6).


Catalyst Elimination (k_4)
NR_3
1
16
Catalyst Addition to Allenoate (k_1)
Possible Rate-Determining Step
Proton Transfer (k_3)
17
C-C Bond Formation with Imine (k_2)

Scheme 31.6

31.2.2
Phosphine Catalyzed Mechanism

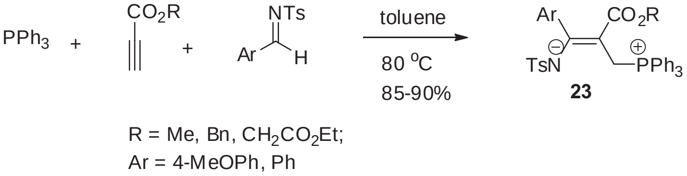
The most likely mechanism of the MBH reaction catalyzed by tertiary phosphines is identical to that of the amine-catalyzed reaction except that the initially formed zwitterion **18** can isomerize to phosphorus ylide **19**, which can then undergo a Wittig reaction to give olefins **20** (Scheme 31.7). The latter process may require elevated temperatures, since it is not observed in reactions such as the MBH reaction involving the more reactive α,β-unsaturated ketones under mild conditions.



Scheme 31.7

Sunoj and coworkers have also carried out theoretical investigations on the mechanism of the trimethylphosphine-catalyzed aza-MBH reaction between acrolein and mesyl imine [17b]. They found that the relative energies of the crucial transition states for the PMe_3-catalyzed reaction are lower than those of the corresponding NMe_3-catalyzed reaction and the kinetic advantage of the PMe_3-catalyzed reaction is also evident in the proton transfer step, where the energies of the transition states are much lower than those of the corresponding NMe_3-catalyzed reaction. These predictions are consistent with the available experimental reports where faster reaction rates are in general noticed for the phosphine-catalyzed aza-MBH reaction [21].

Most recently, Tong *et al.* isolated the stable phosphonium–enamine zwitterion **23**, which has long been postulated as one of the key intermediates in the aza-MBH reaction, from the PPh_3-catalyzed reaction between propiolate and *N*-tosylimine (Scheme 31.8), providing experimental evidence to support the postulated reaction mechanism of the phosphine-catalyzed MBH reaction [22].

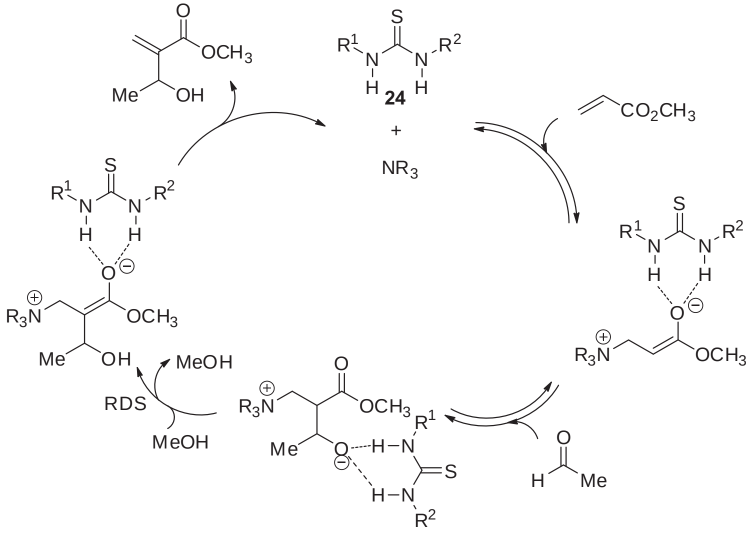


Scheme 31.8

31.2.3

Mechanistic Insights into the MBH/aza-MBH Reaction Using Co-catalytic Systems or Multi-/Bifunctional Catalysts

Besides using traditional Lewis base catalysts in the MBH/aza-MBH reaction, co-catalysts have been often used in the MBH/aza-MBH reaction to accelerate the reaction. Recently, several mechanistic studies have investigated the mechanism of the MBH/aza-MBH reaction using co-catalytic systems. Eberlin and Coelho studied the MBH reaction between 2-thiazolecarboxaldehyde and methyl acrylate in the presence of DABCO and thiourea by ESI-MS(/MS) and DFT techniques [23]. The key intermediates were intercepted and characterized by ESI-MS(/MS) and suggested that thiourea **24** acted as an organocatalyst in all steps of the MBH reaction cycle shown in Scheme 31.9, including the rate-limiting proton-transfer step. The DFT calculations confirmed this suggested catalytic cycle and also revealed that the thiourea did not act as a proton shuttle in the rate-limiting proton-transfer step, instead it acted as a Brønsted acid stabilizing the basic oxygen center being formed in the transition state and decreased the barrier of the RDS, thus accelerating the reaction.



Scheme 31.9

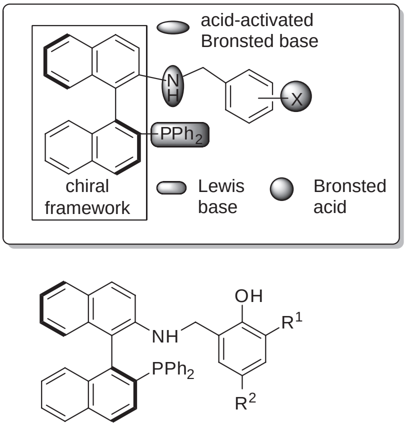
Sunoj and coworker have identified the role of protic co-catalysts such as water, methanol, and formic acid in the MBH/aza-MBH reaction by theoretical studies [17b]. They found that the protic co-catalysts have a profound influence in decreasing the activation barriers associated with the key elementary steps due to the improved stabilization of the proton transfer transition state through a relay mechanism.

The MBH/aza-MBH reaction involving proline as a catalyst with imidazole as a co-catalyst was proposed to proceed through an iminium ion intermediate.

Recently, Santos and coworkers have studied the mechanism of proline-catalyzed and imidazole-co-catalyzed intramolecular MBH reactions by DFT calculations [24]. They first investigated the catalytic path for the MBH reaction of α,β-unsaturated dialdehyde catalyzed by L-proline in the absence of imidazole, and found that water acted as an important catalyst when imidazole was not present. When imidazole was used as a co-catalyst, water was still important in the imidazole addition step. Their results rationalized the experimental outcome of the intramolecular MBH reaction, and provided theoretical evidence for some mechanistic proposals.

Oh and coworkers have performed a mechanistic investigation on the proline-catalyzed asymmetric MBH reactions of vinyl ketones in the presence of brucine *N*-oxide as a co-catalyst [25]. In this dual catalytic system, proline forms iminium intermediates with electron-deficient aryl aldehydes, while the *N*-oxide activates vinyl ketones to provide enolates through conjugate addition. Upon the combination of these two intermediates, MBH products with high enantioselectivities are obtained by controlling the RDS through a H-bridged chair-like transition state. Intrinsically, the resulting MBH products, alcohols, are found to interfere with the formation of both intermediates (enolates and proline-iminium intermediates) and, thus, the observed enantioselectivity of products attenuates upon further reaction conversion, possibly due to autocatalysis.

The bifunctional strategy has been successfully used to design new organocatalysts for the MBH/aza-MBH reaction. In the bifunctional strategy, a Lewis base and a Brønsted acid can be crafted onto one chiral backbone to act cooperatively in the MBH reaction cycle. The Lewis base functionality serves to initiate the Michael addition step of the reaction, and the Brønsted acidity is thought to stabilize the zwitterionic intermediates and promote the subsequent aldol and proton-transfer-elimination step. Recently, Liu and coworkers developed this strategy and employed a trifunctional catalyst (**25**, Figure 31.1), which involves



25a: $R^1 = H$, $R^2 = H$

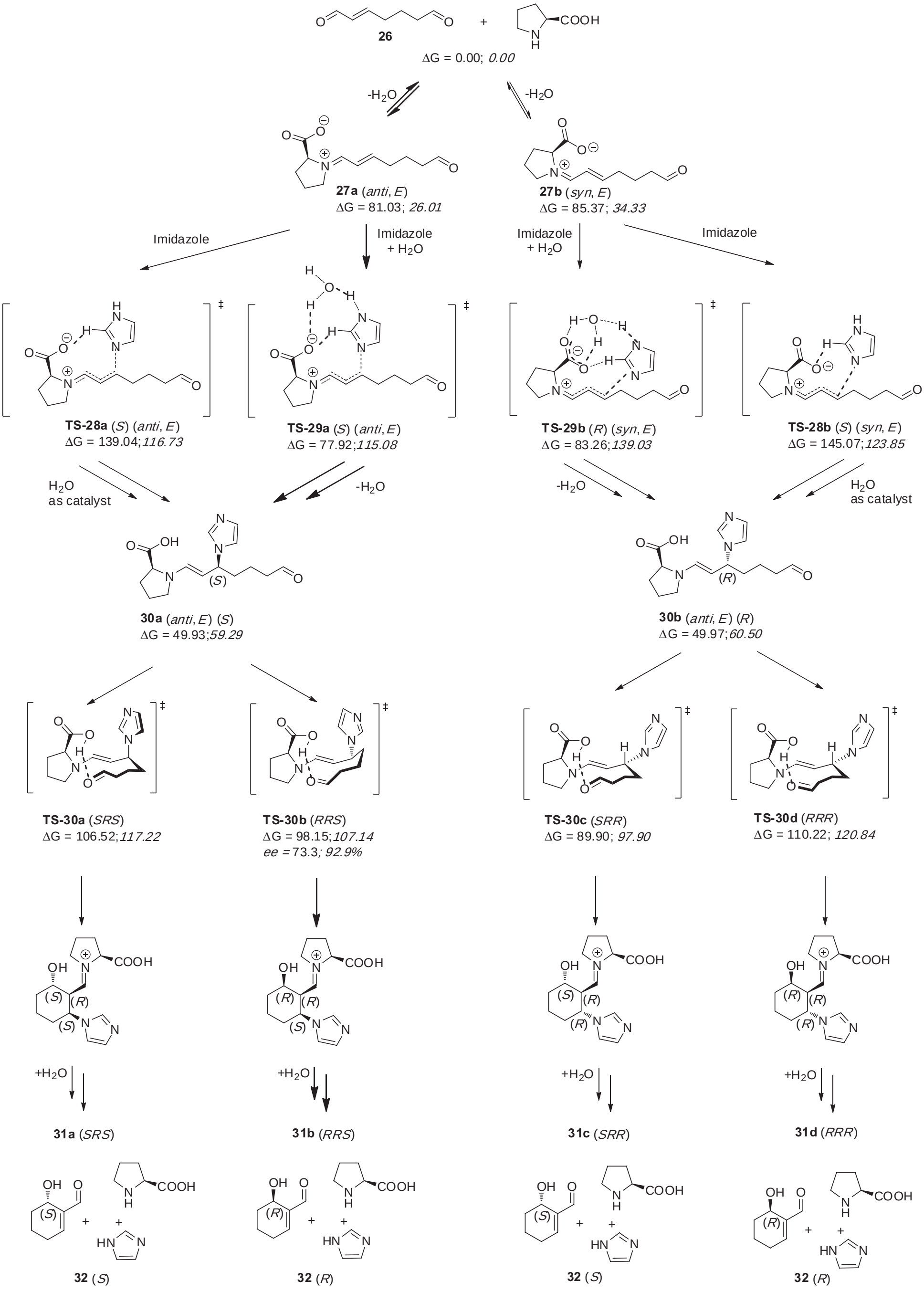
Figure 31.1 Example of a multifunctional catalyst.

the phosphine Lewis base, the nitrogen Brønsted base, and the phenolic Brønsted acid, in the asymmetric aza-MBH reaction [26]. They performed kinetic experiments to investigate the mechanism of the asymmetric aza-MBH reaction catalyzed by the trifunctional catalyst. The catalysis was found to be first order in the trifunctional catalyst with the Michael addition as the rate-limiting step.

31.2.4
Stereoselectivity of the MBH/aza-MBH Reaction

The MBH/aza-MBH product has only one stereogenic center; however, several intermediates and transition states during the reaction have more than one chiral center, which makes studies on the stereoselectivity of MBH/aza-MBH reaction more complicated. Aggarwal proposed a model that first shed light on the asymmetric catalysis of MBH reaction [15]. They suggested that all four diastereomers of the intermediate alkoxide are formed in the reaction, but only one has the hydrogen-bond donor suitably positioned to allow fast proton transfer, while the other diastereomers revert back to starting materials. Although several mechanistic studies also proposed similar transition states to account for the stereoselectivity of MBH/aza-MBH reactions, no studies have investigated the full reaction pathway of the enantioselective MBH/aza-MBH reaction until recently. Santos and coworkers have first investigated proline-catalyzed and imidazole-co-catalyzed enantioselective intramolecular MBH reaction by DFT calculations [24]. Their results indicated that proline played an important role for selectivity in two different reaction steps, the cyclization and the addition of imidazole (Scheme 31.10). They also demonstrated that the imidazole addition step was the rate-limiting step and overall selectivity of the reaction was a result of the selectivities calculated for the imidazole addition and cyclization steps.

Hu and coworker investigated the mechanism of the MBH reaction between formaldehyde and methyl vinyl ketone (MVK) catalyzed by *N*-methylprolinol using the DFT method [16c]. They focused on two steps: C–C bond formation and hydrogen migration, which were considered as the RDSs under different reaction conditions, to investigate the stereoselectivity. In the presence of water, hydrogen migration occurs via a six-membered ring transition state and the corresponding energy barrier decreases dramatically, and therefore the RDS is the C–C bond formation step. The calculations indicate that the C–C bond formation step controls the stereochemistry of the reaction. In this step, the hydrogen bonding induces the direction of the attack of enamine to aldehyde from the -OH group side of *N*-methylprolinol. The energy-favored transition states are mainly stabilized by hydrogen bonding, while the chirality of the products is affected by the hydrogen bonding and the steric hindrance. The calculations correctly reproduce the major product in (*R*)-configuration, which is consistent with experimental observation.

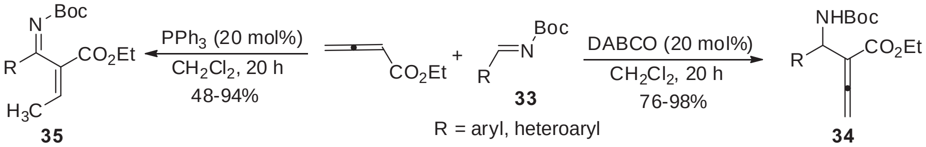


Scheme 31.10 Proposed catalytic paths with reaction intermediates and transition states computationally for the L-proline/imidazole-catalyzed formation of (*R*)-**32.** Free energy (kJ mol^{-1}) calculated at 0 °C at the B3LYP/6-31G(d,p) (plain text) and PCM B3LYP/6-31++G(d,p)B3LYP/6-31G(d,p) (*italic*) levels of theory. The lowest-energy reaction path is indicated by bold arrows.

31.3
Recent Developments of Essential Components

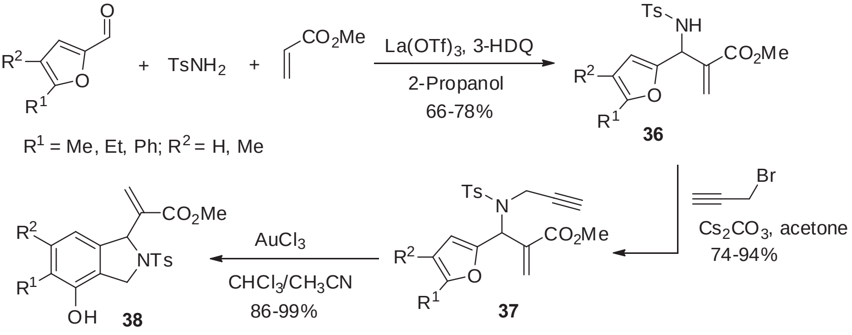
The MBH/aza-MBH reactions have seen tremendous growth in terms of three components, that is, the activated olefins, electrophiles, and catalysts or catalytic systems during the past 40 years. Recently, several research papers descibed applications of novel activated olefins, electrophiles, or catalysts in MBH/aza-MBH reactions.

Shi's group reported the different reactivity patterns shown by nitrogen- and phosphorus-containing Lewis bases as catalysts in the reactions of *N*-Boc-imines **33** with ethyl 2,3-butadienoate, which are different from previous observations in the normal aza-MBH reactions of other imines and beyond the scope of the aza-MBH reactions [27]. The normal aza-MBH products **34** were obtained in good to excellent yields, catalyzed by DABCO, whereas the novel rearrangement product **35** could be formed in moderate yields by using PPh_3 as the catalyst (Scheme 31.11).



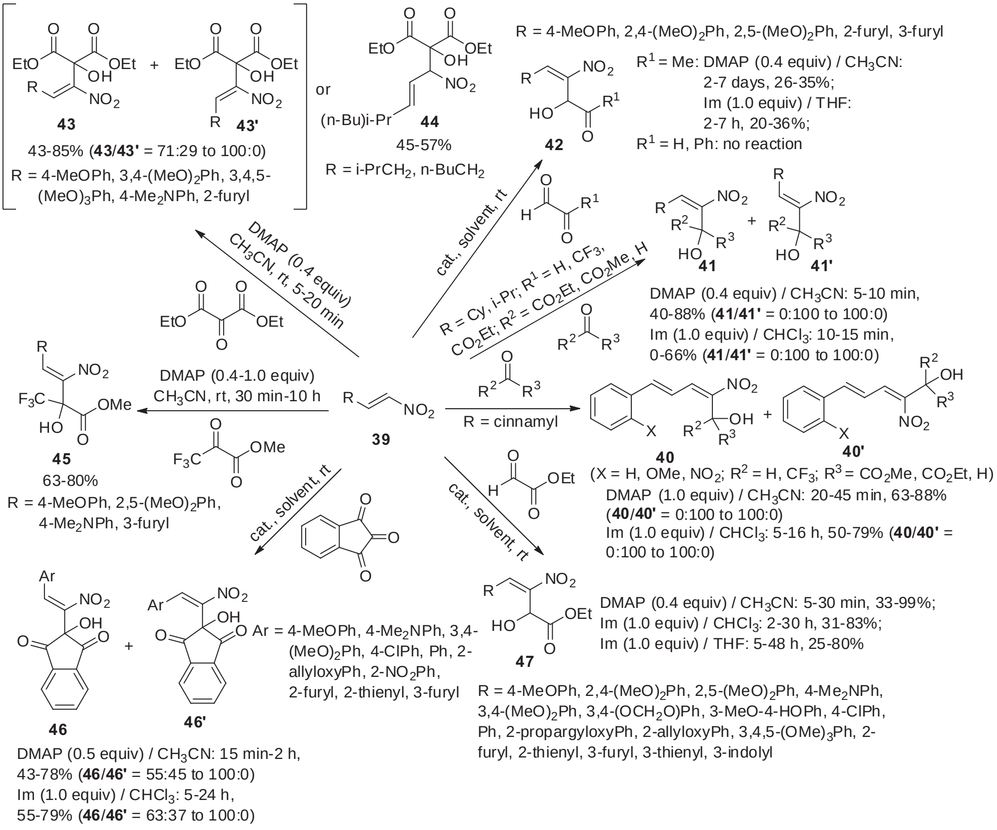
Scheme 31.11

Hashmi *et al.* developed a short and high-yielding synthetic approach toward functionalized indoline derivatives **38** following the reaction sequence, which contained a three-component aza-MBH reaction from furfural catalyzed by $La(OTf)_3$ in combination with 3-HDQ, a simple sulfonamide propargylation, and a gold-catalyzed cycloisomerization (Scheme 31.12) [28].



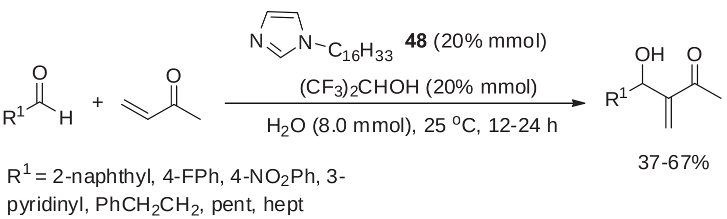
Scheme 31.12

The MBH reactions of various conjugated nitroalkenes **39** with activated non-enolizable carbonyl compounds such as glyoxylate, trifluoropyruvate, pyruvaldehyde, oxomalonate, ninhydrin, and formaldehyde proceeded smoothly in the presence of DMAP (40–100 mol%) in acetonitrile or imidazole (100 mol%) in $CHCl_3$ or THF, providing the multifunctional adducts in good to excellent yields (Scheme 31.13) [29]. In most cases, the reactions catalyzed by DMAP in acetonitrile were superior to the imidazole-catalyzed reactions in terms of the rate of reaction and the isolated yields of the MBH adducts. The catalytic roles played by DMAP and imidazole in these reactions, vis-à-vis other MBH catalysts such as DABCO, are attributed primarily to resonance stabilization of the initial zwitterionic intermediates. Whereas the (*E*)-isomers are the major or exclusive products in the cases of glyoxylate, pyruvaldehyde, and formaldehyde the (*Z*)-isomers predominate in the cases of trifluoropyruvate and ninhydrin. Interestingly, oxomalonate forms (*E*)-isomers with aromatic nitroalkenes and (*Z*)-isomers with aliphatic ones.


43
43'
43-85% (43/43' = 71:29 to 100:0)
R = 4-MeOPh, 3,4-(MeO)2Ph, 3,4,5-(MeO)3Ph, 4-Me2NPh, 2-furyl
or
44
45-57%
R = i-PrCH2, n-BuCH2
R = 4-MeOPh, 2,4-(MeO)2Ph, 2,5-(MeO)2Ph, 2-furyl, 3-furyl
42
R1 = Me: DMAP (0.4 equiv) / CH3CN: 2-7 days, 26-35%;
Im (1.0 equiv) / THF: 2-7 h, 20-36%;
R1 = H, Ph: no reaction
cat., solvent, rt
DMAP (0.4 equiv) CH3CN, rt, 5-20 min
R = Cy, i-Pr; R1 = H, CF3, CO2Et; R2 = CO2Et, CO2Me, H
41
41'
DMAP (0.4 equiv) / CH3CN: 5-10 min, 40-88% (41/41' = 0:100 to 100:0)
Im (1.0 equiv) / CHCl3: 10-15 min, 0-66% (41/41' = 0:100 to 100:0)
DMAP (0.4-1.0 equiv) CH3CN, rt, 30 min-10 h
45
63-80%
R = 4-MeOPh, 2,5-(MeO)2Ph, 4-Me2NPh, 3-furyl
39
R = cinnamyl
40
40'
(X = H, OMe, NO2; R2 = H, CF3; R3 = CO2Me, CO2Et, H)
DMAP (1.0 equiv) / CH3CN: 20-45 min, 63-88% (40/40' = 0:100 to 100:0)
Im (1.0 equiv) / CHCl3: 5-16 h, 50-79% (40/40' = 0:100 to 100:0)
cat., solvent, rt
cat., solvent, rt
46
46'
Ar = 4-MeOPh, 4-Me2NPh, 3,4-(MeO)2Ph, 4-ClPh, Ph, 2-allyloxyPh, 2-NO2Ph, 2-furyl, 2-thienyl, 3-furyl
DMAP (0.5 equiv) / CH3CN: 15 min-2 h, 43-78% (46/46' = 55:45 to 100:0)
Im (1.0 equiv) / CHCl3: 5-24 h, 55-79% (46/46' = 63:37 to 100:0)
47
DMAP (0.4 equiv) / CH3CN: 5-30 min, 33-99%;
Im (1.0 equiv) / CHCl3: 2-30 h, 31-83%;
Im (1.0 equiv) / THF: 5-48 h, 25-80%
R = 4-MeOPh, 2,4-(MeO)2Ph, 2,5-(MeO)2Ph, 4-Me2NPh, 3,4-(MeO)2Ph, 3,4-(OCH2O)Ph, 3-MeO-4-HOPh, 4-ClPh, Ph, 2-propargyloxyPh, 2-allyloxyPh, 3,4,5-(OMe)3Ph, 2-furyl, 2-thienyl, 3-furyl, 3-thienyl, 3-indolyl

Scheme 31.13

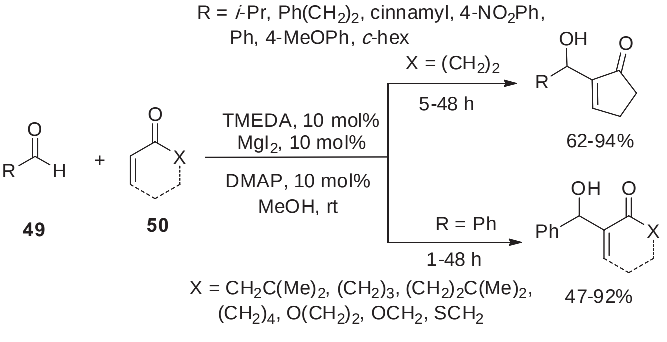
Recently, Matsubara and Asano developed the first example of a "catalytic" MBH reaction of MVK with various aldehydes by using an amphiphilic *N*-alkylimidazole derivative (**48**) carrying a hydrophobic group as organocatalyst in water without organic solvents [30]. This reaction is accelerated by the addition of water and the yields can be improved by addition of catalytic amount of the Brønsted acid, 1,1,1,3,3,3-hexafluoropropan-2-ol, as co-catalyst (Scheme 31.14). It was assumed that the amphiphilic catalyst forms a hydrophobic field for an organic reaction near the boundary between the water and the organic compounds by self-assembly, which shows that such a reaction field constructed by an amphiphilic organocatalyst near the surface of water may be widely effective for the acceleration of organocatalytic reactions.



$N-C_{16}H_{33}$
48 (20% mmol)
$(CF_3)_2CHOH$ (20% mmol)
H_2O (8.0 mmol), 25 °C, 12-24 h
O
R^1
H
+
O
OH O
R^1
37-67%
R^1 = 2-naphthyl, 4-FPh, 4-NO_2Ph, 3-pyridinyl, $PhCH_2CH_2$, pent, hept

Scheme 31.14

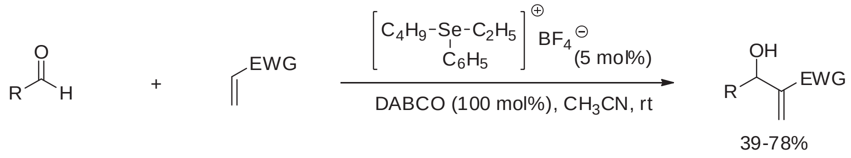
Connell and Bugarin *et al.* found that, by using a catalytic amount of 4-dimethylaminopyridine (DMAP) as a nucleophile in the presence of an equal amount of tetramethylethylenediamine (TMEDA) and MgI_2, MBH adducts can be obtained in good to excellent yields from various aromatic and aliphatic aldehydes **49** and cyclic enones/enoates **50** at room temperature after convenient reaction times (Scheme 31.15) [31].



R = *i*-Pr, $Ph(CH_2)_2$, cinnamyl, 4-NO_2Ph, Ph, 4-MeOPh, *c*-hex
X = $(CH_2)_2$
5-48 h
OH O
R
62-94%
O
R
H
+
O
X
49
50
TMEDA, 10 mol%
MgI_2, 10 mol%
DMAP, 10 mol%
MeOH, rt
R = Ph
1-48 h
OH O
Ph
X
47-92%
X = $CH_2C(Me)_2$, $(CH_2)_3$, $(CH_2)_2C(Me)_2$, $(CH_2)_4$, $O(CH_2)_2$, OCH_2, SCH_2

Scheme 31.15

The new acidic ionic liquid phenyl(butyl)(ethyl)selenonium tetrafluoroborate, [pbeSe]BF_4, was found to be a new acid co-catalyst and successfully used in the MBH reaction of several electron-deficient alkenes with aromatic and aliphatic aldehydes in moderate to good yields and in relatively short reaction times under mild conditions (Scheme 31.16) [32].

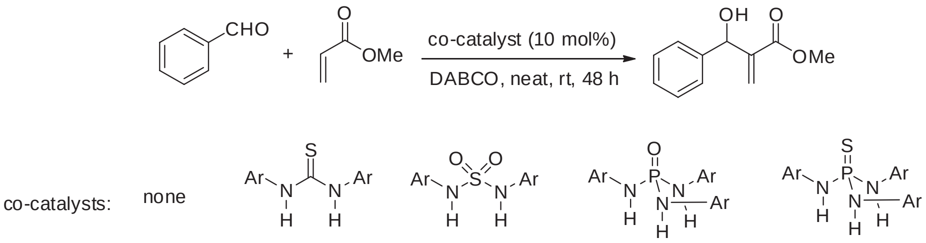


R = Ph, 2-furyl, pent, hex

EWG = CO_2Me, CN, COMe, $CO(CH_2)_3$

Scheme 31.16

Shea *et al.* synthesized three new achiral sulfamide **51**, phosphoric triamide **52**, and thiophosphoric triamide **53** as hydrogen bond catalysts for the MBH reaction. It was found that each of these three compounds showed activity and modest improvements (1.5-fold) for selected MBH reaction when compared to the corresponding thiourea catalyst **24**, which shows the possibility for the development of new, more efficient MBH catalysts (Scheme 31.17) [33].



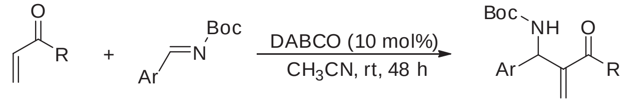
co-catalysts:	none	**24**	**51**	**52**	**53**
k_{rel}	0.5	1.0	1.5	1.1	1.3
% conv.	32	58	73	59	67

Ar = 3,5-$(CF_3)_2C_6H_3$

Scheme 31.17

Shi and coworkers have developed DABCO-catalyzed aza-MBH reactions of *N*-Boc imines with methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) [34]. As shown in Scheme 31.18, whether electron-withdrawing or electron-donating groups at the *ortho-*, *meta-*, or *para*-position of the benzene ring of *N*-Boc imines

33 were employed, the reactions proceeded smoothly to give *rac*-**54** in moderate to good yields. EVK was also examined in this reaction, giving the corresponding product in 35% yield. Unfortunately, this reaction was not suitable for alkyl *N*-Boc imines.



33

54-rac

R = Me, Et

Ar = p-$CF_3C_6H_4$, p-FC_6H_4, p-BrC_6H_4, p-$MeOC_6H_4$, p-MeC_6H_4, m-MeC_6H_4, m-ClC_6H_4, o-$MeOC_6H_4$, o-ClC_6H_4, 2-furyl, C_6H_5

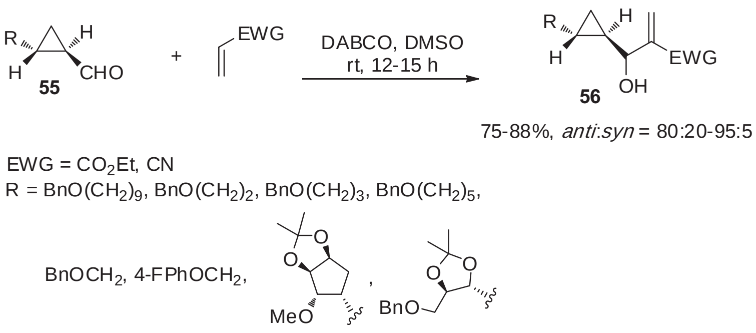
Yield% = 35-82%

Scheme 31.18

31.4
Recent Developments of Asymmetric MBH/aza-MBH Reactions

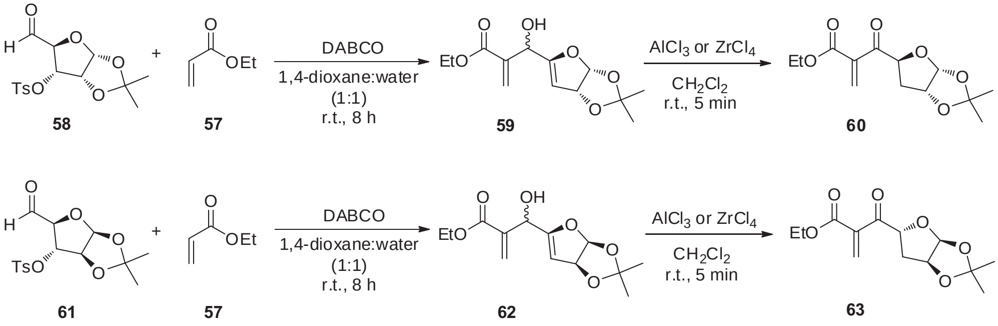
31.4.1
Asymmetric Induction with Substrates

Krishna and coworkers first reported that chiral aldehydes *trans*-(2*R*,3*R*)-cyclopropanecarbaldehydes **55** underwent a facile MBH reaction with various activated olefins in the presence of a catalytic amount of DABCO to furnish the corresponding adducts **56** in good yields and selectivities (Scheme 31.19) [35]. It was found that the ring conformation and substituents played a decisive role in the stereoselection of the product. Subsequently, they reported an innovative synthesis of 3-deoxy sugars in both D and L forms as exclusive products in high yield through a sequential MBH reaction of sugar-derived aldehyde with ethyl acrylate and Lewis acid catalyzed reaction [36]. It was demonstrated that an aldehyde carrying a



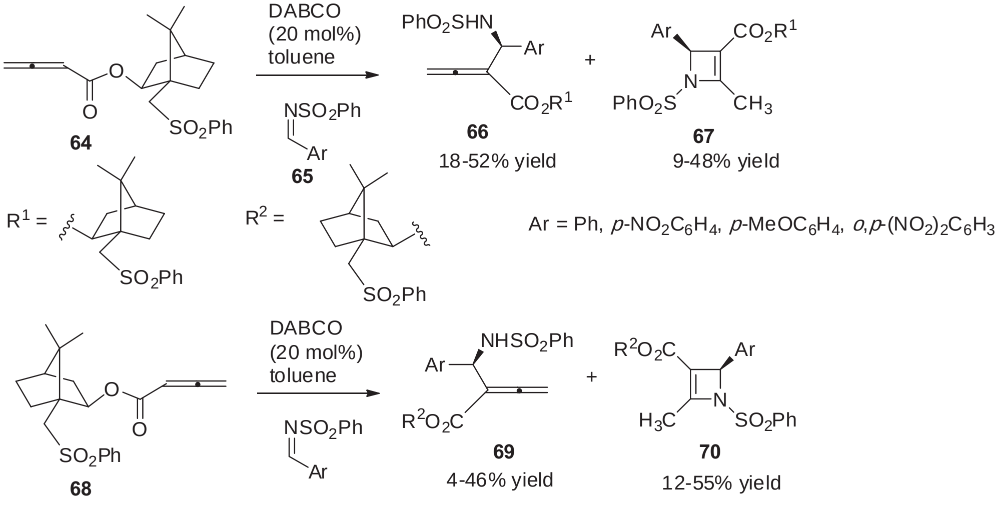
Scheme 31.19

properly positioned leaving group when subjected to the DABCO-catalyzed MBH reaction can be converted into divinyl carbinols, which upon exposure to Lewis acid afforded the corresponding 3-deoxy sugars as exclusive isomers in high yields (Scheme 31.20). These products would also serve as valuable components in the synthesis of sugar-modified nucleosides.



Scheme 31.20

Pinho e Melo *et al.* have demonstrated a DABCO-catalyzed aza-MBH reaction of chiral allenes with imine to synthesize optically active α-allenylamines and 2-azetine derivatives [37]. The use of (1*R*)-(–)-10-phenylsulfonylisobornyl buta-2,3-dienoate as a starting material affords products with an (*S*)-configuration, whereas (1*S*)-(+)-10-phenylsulfonylisobornyl buta-2,3-dienoate leads to products with a (*R*)-configuration (Scheme 31.21). The yields of products and the ratio of product **66**:**67** and **69**:**70** can be controlled by carefully selecting the reaction conditions or by tuning the electronic properties of the imine.

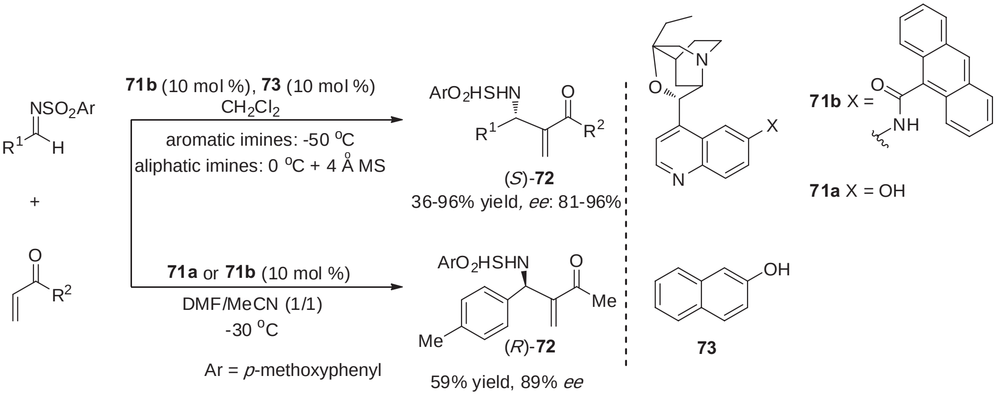


Scheme 31.21

31.4.2
Catalytic Asymmetric Induction with Chiral Lewis Bases

31.4.2.1 Chiral Tertiary Amine Catalysts

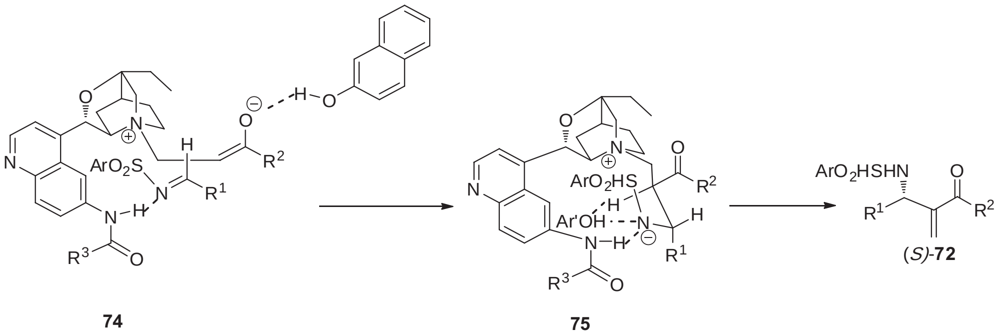
Chiral tertiary amine catalysts based on the quinidine framework such as β-isocupreidine (β-ICD) for asymmetric MBH/aza-MBH reactions have been investigated intensively. Recent studies demonstrate that β-isocupreidine (β-ICD) is still an efficient chiral catalyst with good selectivity for asymmetric MBH/aza-MBH reactions with respect to various substrates. Zhu's group reported a β-ICD (**71a**) or β-ICD-amide (**71b**) catalyzed aza-MBH reaction between *N*-sulfonylimines and alkyl vinyl ketones, affording (*R*)-enriched product **72** [38]. Interestingly, they found that adding a catalytic amount of β-naphthol (**73**) led to the same reaction with reversed enantioselectivities, affording the product (*S*)-**72** in excellent yields and enantioselectivities (Scheme 31.22). This reaction was suitable for aromatic imines and aliphatic imines. The authors hypothesized that the Mannich-type coupling step may become the rate-determining step in the presence of achiral protic additive β-naphthol in this reaction, affording the (2*S*,3*S*) Mannich adduct **75** via ternary (*Z*)-enolate complex **74.** Subsequent β-naphthol-assisted β-elimination of (2*S*,3*S*) Mannich adduct **75** would, via a plausible six-membered cyclic transition state, then provide the observed (*S*)-aza-MBH adduct **72** (Scheme 31.23). The authors also performed a control experiment that indicated that both the amide-NH in **71b** and phenol-OH in **73** were important for the high enantioselectivity observed in this catalytic system. Subsequently, Zhu's group reported another β-ICD-amide catalyzed and β-naphthol co-catalyzed aza-MBH



R^1 = p-MeC_6H_4, p-$MeOC_6H_4$, p-$CF_3C_6H_4$, p-ClC_6H_4, m-BrC_6H_4, o-BrC_6H_4, PhCH=CH, C_6H_5, $i$$PrCH_2$, c-hexylCH_2, n-butyl, $Ph(CH_2)_2$, n-pentyl

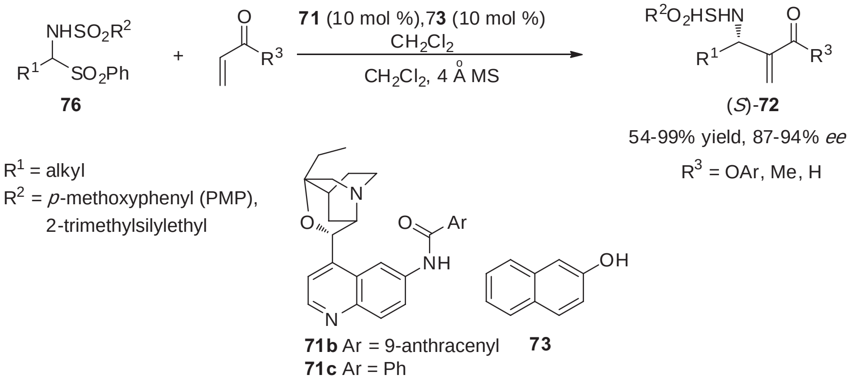
R^2 = Me, Et

Scheme 31.22



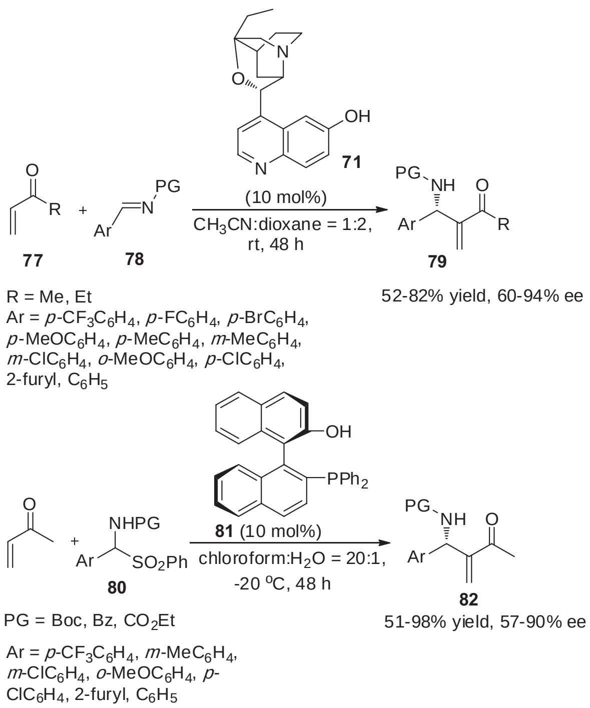
Scheme 31.23

reaction using readily available α-amidosulfones **76** as substrates to afford uniformly the (*S*)-adducts in high yields and excellent enantioselectivities (Scheme 31.24) [39]. This is a domino process in which the catalyst **71** served both as a base to trigger the *in situ* generation of *N*-sulfonylimine and then as a nucleophile to initiate the aza-MBH reaction. This reaction proceeded smoothly with respect to various substrates under mild reaction conditions, providing an easy access to α-methylene-β-amino-β-alkyl carbonyl compounds with simple operations.



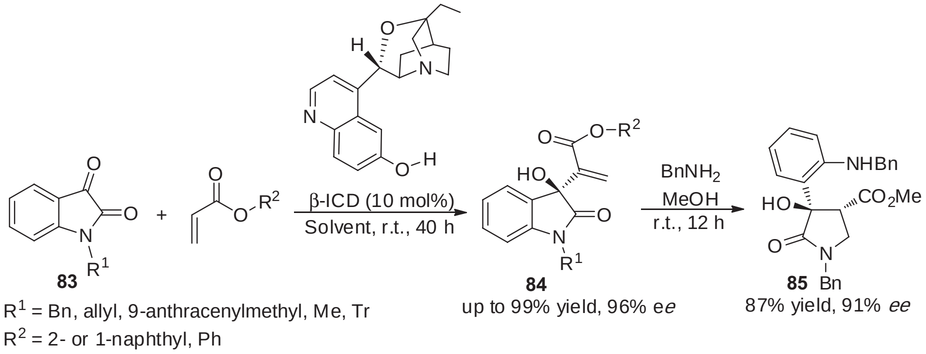
Scheme 31.24

Shi and coworkers almost simultaneously demonstrated the similar asymmetric aza-MBH reaction of N-protected imines **78** or N-protected α-amidoalkyl phenyl sulfones **80** with MVK catalyzed by β-ICD or catalyst **81**, affording highly enantioselective aza-MBH products in good yields with high enantioselectivities (Scheme 31.25) [34]. Besides mild reaction conditions and operational simplicity since it avoided the handing of unstable preformed imines, the reaction was found to be general with respect to various N-protected imines. Subsequently, Shi's group reported a β-ICD-catalyzed asymmetric MBH reaction of isatin derivatives **83** with



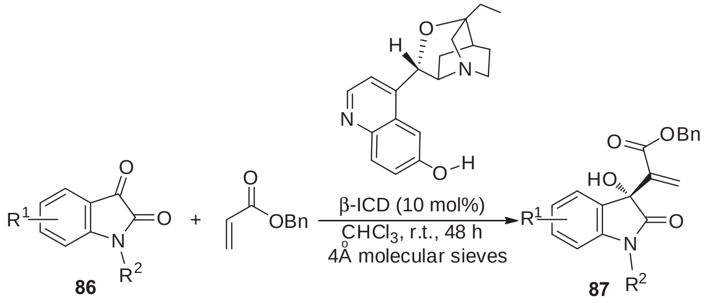
Scheme 31.25

acrylates to afford 3-substituted 3-hydroxy-2-oxindoles **84** in good yields with high enantioselectivities (Scheme 31.26) [40]. This is the first example to employ isatin derivatives in the MBH reaction, demonstrating an efficient synthetic method for the catalytic asymmetric construction of a quaternary stereocenter. The obtained MBH adducts, 3-substituted 3-hydroxy-2-oxindoles, could be facilely transformed into 3-aryl-3-hydroxypyrrolidin-2-ones **85** (with chirality remaining), which were precursors of promising drug candidates for treatment of HIV-1 infection.



Scheme 31.26

Recently, Lu's group reported almost the same β-ICD-catalyzed asymmetric MBH reaction of isatin derivatives with acrylates [41]. They also demonstrated that β-ICD was an efficient catalyst for this reaction, affording 3-substituted 3-hydroxy-2-oxindoles **87** in good yields with high enantioselectivities (Scheme 31.27). They pointed out that the C6′-OH group of β-ICD probably facilitates the key proton transfer step in the MBH reaction, via an intramolecular proton relay process. Zhou and coworkers also demonstrated a β-ICD catalyzed MBH reaction of isatins and acrolein to provide enantiomerically enriched 3-substituted 3-hydroxyoxindoles **89**, which could serve as valuable synthetic building blocks [42]. Various isatins with acrolein underwent this reaction smoothly to give the MBH adducts with excellent ee (Scheme 31.28). The obtained MBH adducts could be easily transformed into other compounds that can be potentially used for the synthesis of analogues of natural products.

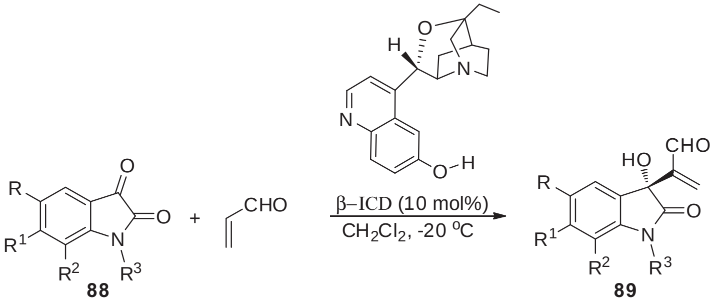


up to 96% yield, 96% ee

R^1 = H, 7-Cl, 7-F, 5-F, 5-Cl, 5-Br, 5-NO_2, 5-Me, 5-OMe, 5,7-Me

R^2 = Bn, *p*-OMe-Bn, $CHPh_2$, CPh_3, Ph, *p*-OMe-Ph, Me

Scheme 31.27

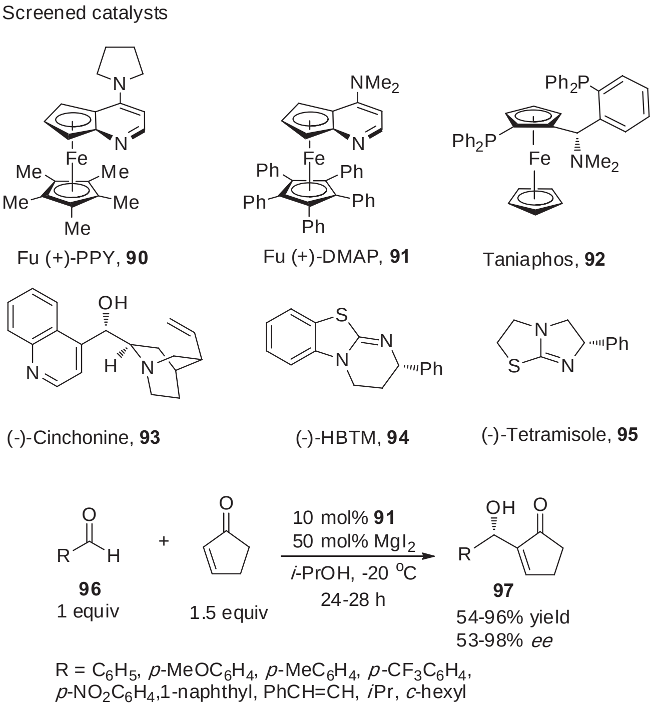


65-97% yield, 90-99% ee

R = H, F, Cl, Br, Me, MeO, NO_2, CF_3
R^1 = H, Br
R^2 = H, Cl, Br
R^3 = H, Me, Bn

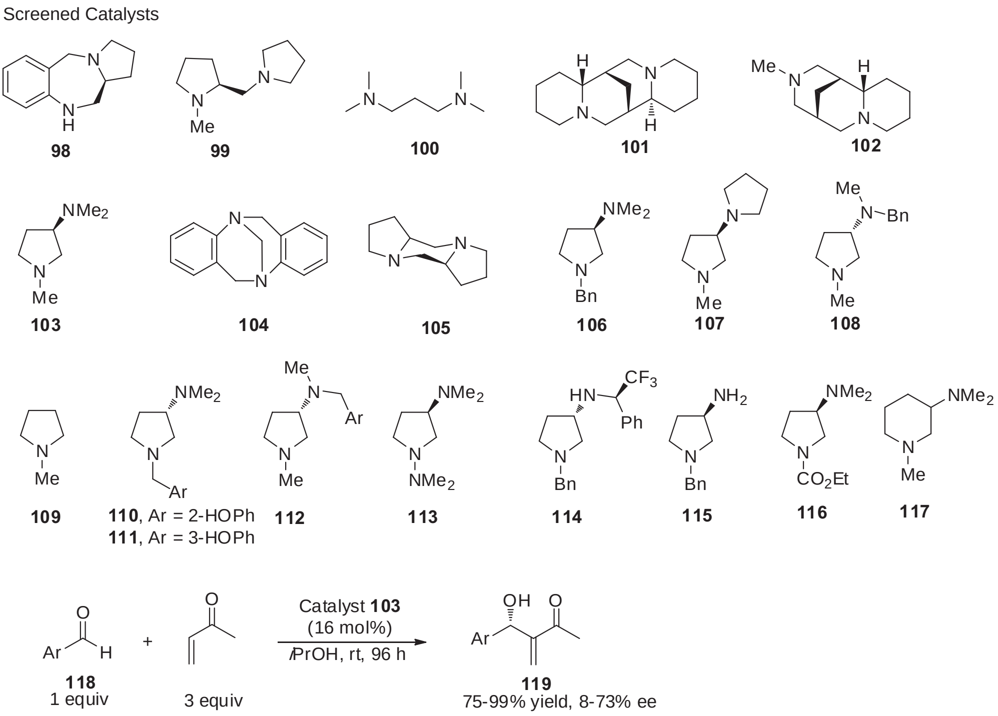
Scheme 31.28

Recently, Connell and coworker screened a series of chiral amine nucleophiles (**90–95**) for the asymmetric MBH reaction of aromatic and aliphatic aldehydes with cyclopentenone in the presence of MgI_2 (Scheme 31.29) [43]. They identified Fu's planar chiral DMAP catalyst **91** as the most efficient catalyst for this asymmetric MBH reaction, affording the products **97** in good to excellent yields and moderate to excellent enantioselectivities. Both aromatic aldehydes and aliphatic aldehydes were suitable for this reaction. They also pointed out that MgI_2 as a co-catalyst could accelerate the reaction rate.



Scheme 31.29

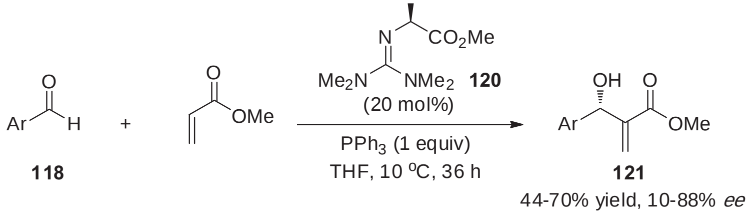
Rouden and Maddaluno screened 20 new and easily prepared diamines **98–117** for the asymmetric MBH reaction of MVK and substituted benzaldehydes (Scheme 31.30) [44]. Chiral non-racemic 3-(*N,N*-dimethylamino)-1-methylpyrrolidine **103** was found to promote the reaction efficiently. Enantiomeric excesses up to 73% were reached with electron-deficient benzaldehyde derivatives. After a simple deprotonation, one of these diamines was transformed into a chiral mixed aggregate for the enantioselective synthesis of (*R*)-1-*o*-tolylethanol with 76% ee.



Ar = 2-NO$_2$-C$_6$H$_4$, 2-CF$_3$-C$_6$H$_4$, 2,4-Cl-C$_6$H$_3$,
4-CF$_3$-C$_6$H$_4$, 4-CO$_2$Me-C$_6$H$_4$, 4-CN-C$_6$H$_4$,

Scheme 31.30

Liebscher and coworkers have demonstrated a novel dual catalytic system composed of chiral α-guanidino-ester **120** and triphenylphosphine as an efficient catalytic system for asymmetric MBH reactions (Scheme 31.31) [45]. This catalytic system provided good enantioselectivities, up to 88% in the asymmetric MBH reactions of aromatic aldehydes with methyl acrylate. However, other Michael

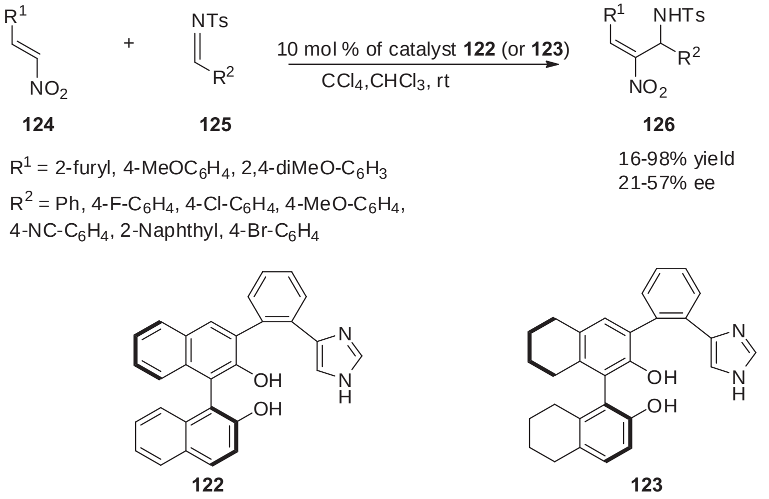


Ar = 4-NO$_2$-C$_6$H$_4$, 2-NO$_2$-C$_6$H$_4$, 4-Cl-C$_6$H$_4$,
4-BrC$_6$H$_4$, C$_6$H$_5$

Scheme 31.31

acceptors such as acrylonitrile or MVK were not suitable substrates for these asymmetric MBH reactions.

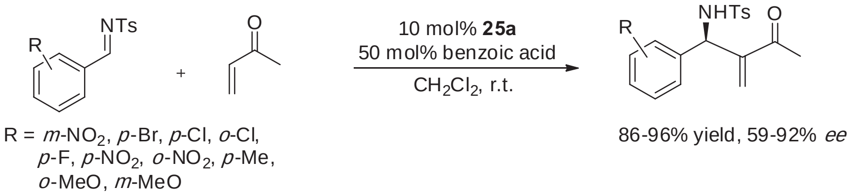
Takizawa and Sasai developed a new class of acid–base chiral organocatalysts (**122** and **123**) bearing an imidazole unit for aza-MBH reaction of conjugated nitroalkenes (Scheme 31.32) [46]. The acidic phenolic hydroxy groups and basic imidazole unit cooperatively activate nitroalkenes to promote the aza-MBH reaction in good yields with moderate enantioselectivities. They also investigated the substrate scope of this catalytic system under the optimized reaction conditions. Regardless of whether the aromatic substituent R^2 of imine **125** is electron-withdrawing or electron-donating, organocatalysts **122** and **123** promoted the reaction. The reactions of 4-methoxy-1-(2-nitrovinyl)benzene and 2,4-dimethoxy-1-(2-nitrovinyl)benzene produced the corresponding adducts but with low yields and enantioselectivities. When using (2-nitrovinyl)benzene as a substrate, no reaction was observed.


R1
NO2
+
NTs
R2
10 mol % of catalyst 122 (or 123)
CCl4,CHCl3, rt
R1
NHTs
R2
NO2
124
125
126
R1 = 2-furyl, 4-MeOC6H4, 2,4-diMeO-C6H3
R2 = Ph, 4-F-C6H4, 4-Cl-C6H4, 4-MeO-C6H4, 4-NC-C6H4, 2-Naphthyl, 4-Br-C6H4
16-98% yield
21-57% ee
OH
OH
N
N
H
122
OH
OH
N
N
H
123

Scheme 31.32

31.4.2.2 **Chiral Tertiary Phosphine Catalysts**

In 2009, Liu's group first used trifunctional chiral phosphanes to catalyze an asymmetric aza-MBH reaction between *N*-tosylimines and MVK with fast reaction rates and good enantioselectivity at room temperature (Scheme 31.33) [47]. This



Scheme 31.33

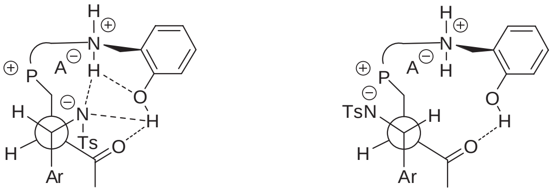


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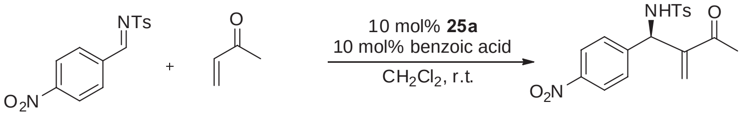
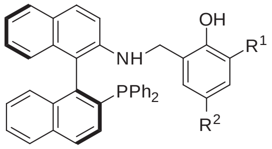
Figure 31.2 Proposed transition structures.

trifunctional catalytic system containing a Lewis base, a Brønsted base, and a Brønsted acid moiety as shown in Figure 31.1 was an extension of a bifunctional catalytic system involving a Lewis base and a Brønsted acid moiety. This catalytic system required an acidic additive such as benzoic acid to confer its enantioselectivity and rate improvement for both electron-rich and electron-deficient imine substrates. A working hypothesis is that activation by benzoic acid after protonation at the nitrogen center, in conjunction with the phenol group, provided the H-bonding network and counterion that are required for the observed catalysis (Figure 31.2, proposed transition structures). In the disfavored transition structure, the proton-transfer step would be slow, and the rate of this pathway does not depend on the presence or absence of an ion pair. The pathway through the favored transition structure, however, is expedited by **25a** only after protonation with benzoic acid to form the required chiral ion pair. The kinetic advantage conferred by a counterion-facilitated proton transfer allows the substrates to pass through this pathway faster than other competing pathways, which is consistent with the observation that the rate enhancement and enantioselectivity arise jointly upon acid activation. Subsequently, the same authors developed a series of trifunctional chiral phosphine catalysts by tuning the acidity of the phenolic Brønsted acid group to improve catalytic efficiency [48]. They found that compared to catalyst **25a** the catalysts **25d** or **25f** with a more acidic phenolic Brønsted acid group are more efficient for the aza-MBH reaction between *N*-tosylimines and MVK (Scheme 31.34). Furthermore, they designed and synthesized a series of new trifunctional catalysts **127b–127e** with a NH_2 or NHTs Brønsted acid moiety, and investigated their performance in generic and aza-MBH reactions [49]. Using catalyst **127d,** better enantioselectivity was observed for aza-MBH reactions at relatively low catalyst loading (2.5 mol%) under facile conditions; the substrate scope of catalyst **127d** was also investigated using a representative set of aryl imines and aryl aldehydes (Scheme 31.35). Catalyst **127d** is generally tolerant of substituted aryl imines, except *ortho*-substituted ones; however, it is limited by the reactivity of aryl aldehydes. The authors also demonstrated that the cooperativity between the counterion and the NHTs Brønsted acid of the trifunctional catalyst was required for good enantioselectivity and rate enhancement.



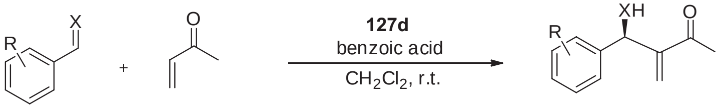
Catalyst	Time/min	Conv. (%)[a]	ee (%)[b]
25a	15	15 (>95%[c])	80
25b	15	85[c]	73
25c	15	57 (87)[d]	81
25d	15	91 (>95)[d]	82
25e	15	87 (>95)[d]	88
25f	15	57 (91)	87

[a]Calculated by H NMR spectroscopy. [b]Determined by chiral HPLC. [c]Conversion after 180 min. [d]Conversion after 30 min in parentheses



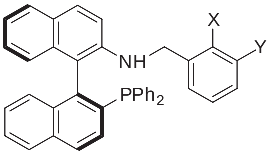
25a: R^1 = H, R^2 = H
25b: R^1 = *t*-Bu, R^2 = H
25c: R^1 = F, R^2 = H
25d: R^1 = *t*-Bu, R^2 = Br
25e: R^1 = F, R^2 = Br
25f: R^1 = *t*-Bu, R^2 = NO_2

Scheme 31.34



R	X	Cat. (mol%)	Time (h)	yield (%)[a]	ee (%)[b]
p-NO_2	NTs	2	2	92	86[c]
p-Br	NTs	2	12	92	81
o-Cl	NTs	5	12	96	54
p-Me	NTs	5	36	93	70[c]
m-NO_2	NTs	2	2	97	86
o-OMe	NTs	5	36	91	60
p-NO_2	O	10	6	73[d]	-
p-Me	O	10	24	-[e]	-

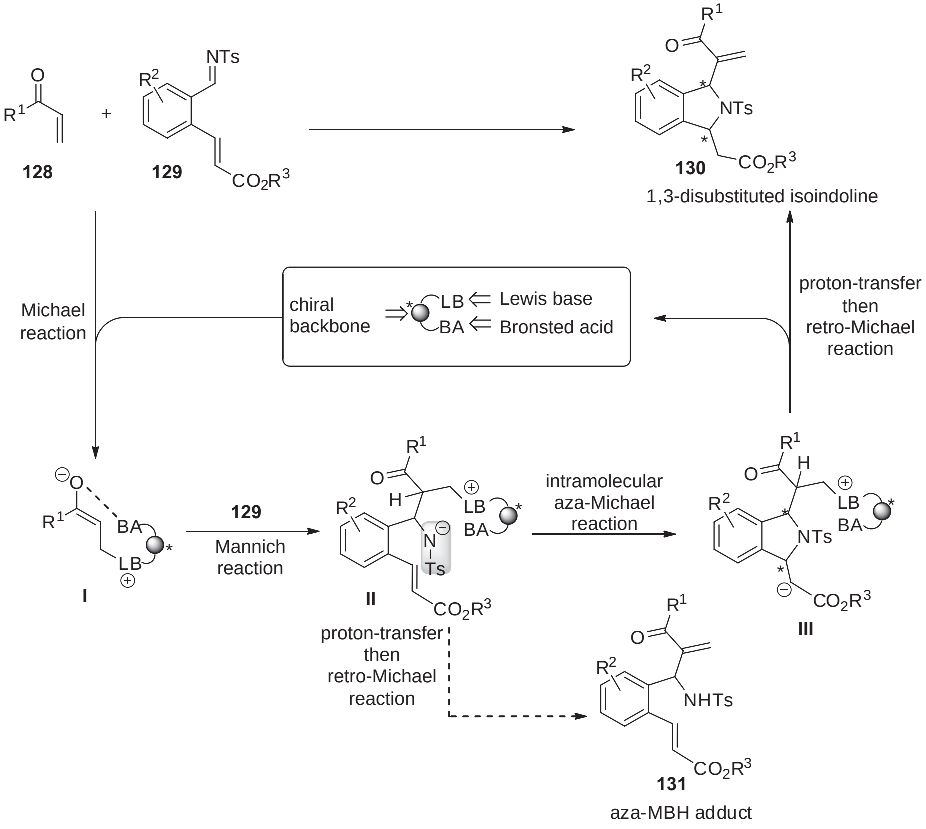
[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]Scale-up reaction at 1 mmol of imine. [d]Calculated by ^1H NMR spectroscopy. [e]No conversion by ^1H NMR spectroscopy.



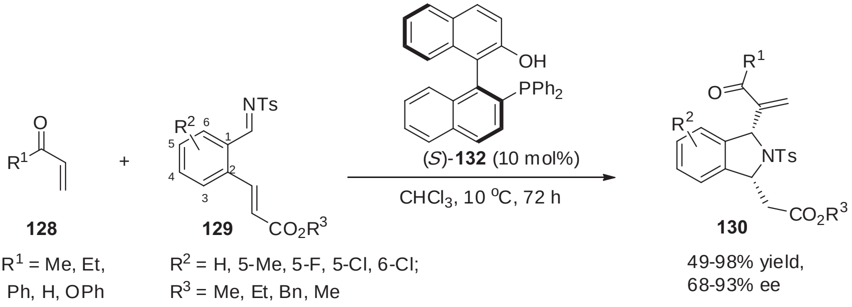
127a: X = H, Y = H
127b: X = NH_2, Y = H
127c: X = H, Y = NHTs
127d: X = NHTs, Y = H
127e: X = OH, Y = NHTs

Scheme 31.35

Sasai reported the first domino process based on the aza-MBH reaction catalyzed by bifunctional chiral phosphine (*S*)-**132** [50]. They envisioned that chiral 1,3-disubstituted isoindoline **130** could be rapidly accessed from enone **128** and *N*-tosylimine **129** with a Michael acceptor moiety at the *ortho* position in the presence of an organocatalyst bearing both Brønsted acid (BA) and Lewis base (LB) units. A proposed catalytic cycle for the aza-MBH domino reaction is shown in Scheme 31.36. In the first step, Michael addition of the Lewis base moiety to enone **128** generates chiral enolate I stabilized by BA; it then reacts with *N*-tosylimine **129** to form intermediate II. In the aza-MBH reaction pathway, proton-transfer from the α position of the carbonyl group to the amine group and subsequent retro-Michael reaction of the organocatalyst proceeds to form the normal aza-MBH adduct **131.** Alternatively, the nitrogen anion of intermediate II could react with the attached Michael acceptor intramolecularly, thus affording the chiral isoindoline **130** via intermediate III along with regeneration of the organocatalyst through proton-transfer and subsequent retro-Michael reaction.


R1
O
128
R2
NTs
129
CO2R3
+
130
CO2R3
1,3-disubstituted isoindoline
Michael reaction
chiral backbone
LB ⇐ Lewis base
BA ⇐ Bronsted acid
proton-transfer then retro-Michael reaction
I
129
Mannich reaction
II
H
LB
BA
N
Ts
intramolecular aza-Michael reaction
III
proton-transfer then retro-Michael reaction
NHTs
131
aza-MBH adduct

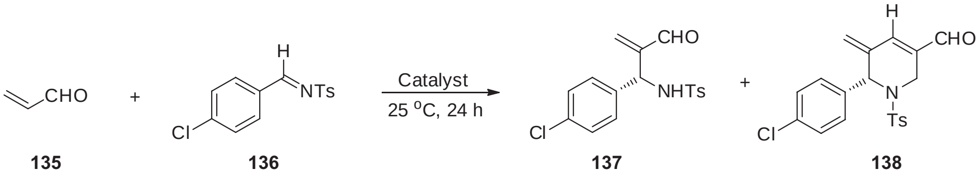
Scheme 31.36



Scheme 31.37

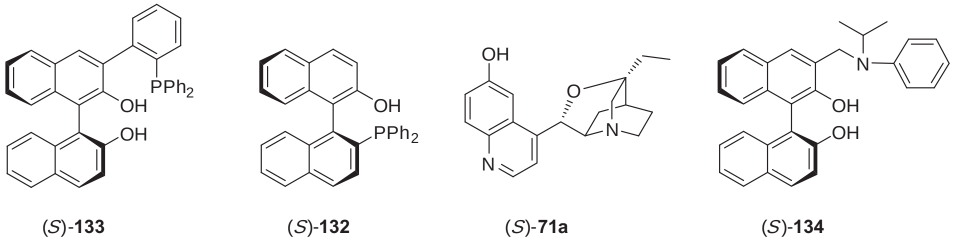
The authors screened a series of commonly used organocatalysts for this enantioselective aza-MBH domino reaction of enone with *N*-tosylimine, and found that acid–base organocatalyst (*S*)-**132** was the most efficient in mediating this reaction. After optimization of the reaction conditions, they investigated the scope of aza-MBH domino reaction catalyzed by (*S*)-**132** and the results are shown in Scheme 31.37. The synthetic utility of the highly functionalized aza-MBH domino product was demonstrated through various transformations. Subsequently, the same authors developed another enantioselective aza-MBH domino process of α,β-unsaturated carbonyl compounds and *N*-tosylimines to afford tetrahydropyridine derivatives [51]. They examined the catalyst (*S*)-**132** and several other known chiral organocatalysts for this an aza-MBH domino process (Scheme 31.38), and found that the acid–base organocatalyst (*S*)-**134** was the most efficient catalyst for this reaction, giving the product in high enantioselectivity. The substrate scope under the optimized reaction conditions was investigated. Regardless of whether the aromatic substituent of **136** is electron-withdrawing or electron-donating, acid–base organocatalyst (*S*)-**134** promotes the reaction, affording products **138** in moderate yields with good to high enantioselectivities (Scheme 31.39). α,β-Unsaturated *N*-tosylimine was also able to be used as a substrate.

Wu and coworkers recently developed a new class of chiral phosphine-squaramide catalysts to promote the asymmetric intramolecular MBH reaction of ω-formylenones [52]. They first tested these newly developed chiral phosphine-squaramide catalysts **139** and several other related phosphine catalysts (**140–142**) (Scheme 31.40) in this intramolecular MBH reaction. The chiral phosphine-squaramides **139a–c**, containing different alkoxyl scaffolds, all exhibited high catalytic activities, and the MBH adducts were obtained in very good yields and enantioselectivities. Subsequently, the substrate scope was explored in the presence of phosphine-squaramide **139a.** As shown in Scheme 31.40, the reactions worked well with acyclic substrates, bearing hydrogen, electron-withdrawing, or electron-donating substituents on the phenyl group, to give the desired adducts in good to high yield (64–98%) and excellent enantioselectivity (88–93% ee).

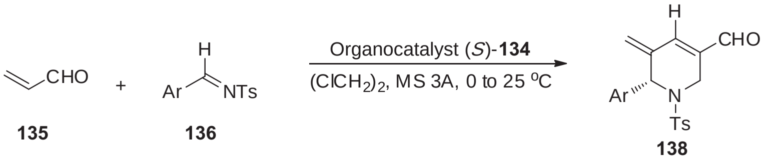


Entry	Catalyst	Solvent	Ratio of **137**:**138**	Yield[b] (%)	Ee[c,d] (%)
1	(*S*)-**133**	$CHCl_3$	100:0	81	9[e]
2	(*S*)-**132**	$CHCl_3$	0:100	27	72
3	(*S*)-**71a**	$CHCl_3$	0:100	27	73
4	(*S*)-**134**	$CHCl_3$	0:100	35	82
5	(*S*)-**134**	THF	96:4	100	81
6	(*S*)-**134**	CPME	99:1	37[f]	81
7	(*S*)-**134**	Toluene	83:17	35[f]	80
8	(*S*)-**134**	CH_2Cl_2	0:100	31	83
9	(*S*)-**134**	$(ClCH_2)_2$	37:63	18	84
10[g]	(*S*)-**134**	$(ClCH_2)_2$	38:62	58	85
11[g,h]	(*S*)-**134**	$(ClCH_2)_2$	98:2	98	92
12[g,i]	(*S*)-**134**	$(ClCH_2)_2$	0:100	60	87

[a] 20 mol% of catalyst was used.
[b] Isolated total yield of **137** and **138**.
[c] Ee of major product.
[d] (*R*)-form.
[f] Unreacted **136** remained.
[g] MS 3Å was added.
[h] At 0 °C for 48 h.
[i] At 0 °C for 48 h then 25 °C for 24 h.



Scheme 31.38

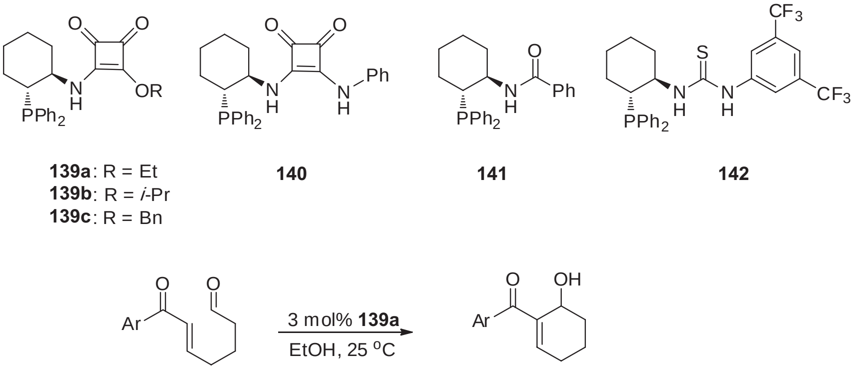


40-60% yield,
75-88% ee

Ar = 3-Cl-C_6H_4, 2-Cl-C_6H_4, 4-NO_2-C_6H_4,
Ph, 3,4-$(MeO)_2$-C_6H_3, 4-NC-C_6H_4, 4-Br-C_6H_4,
(*E*)-PhCH=CH

Scheme 31.39

Screened Catalysts



139a: R = Et
139b: R = *i*-Pr
139c: R = Bn

140

141

142

64-98% yield,
88-93% ee

Ar = C_6H_5, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4,
4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4,
2-MeC_6H_4, 4-$MeOC_6H_4$, 2-Naphthyl

Scheme 31.40

More recently, Lu's group designed and prepared the series of novel bifunctional phosphine-sulfonamide organic catalysts **143–148** from natural amino acids (Figure 31.3), and utilized them to promote enantioselective aza-MBH reactions [53]. L-Threonine-derived phosphine-sulfonamide **148b** was found to be the most efficient catalyst, and the reaction is applicable to a wide range of aromatic imines, affording the desired aza-MBH adducts in high yields and with excellent enantioselectivities (Scheme 31.41). Notably, the *ortho*-substituted aromatic imines, which are well-known as difficult substrates for the aza-MBH reaction, were found to be suitable, and the products were obtained in nearly quantitative yields and with up to 97% ee. These results represent by far the best enantioselectivities attainable for *ortho*-substituted substrates in the aza-MBH reaction. In addition, imines with heterocyclic rings were also applicable. A less satisfactory result was obtained for a cyclohexyl imine.

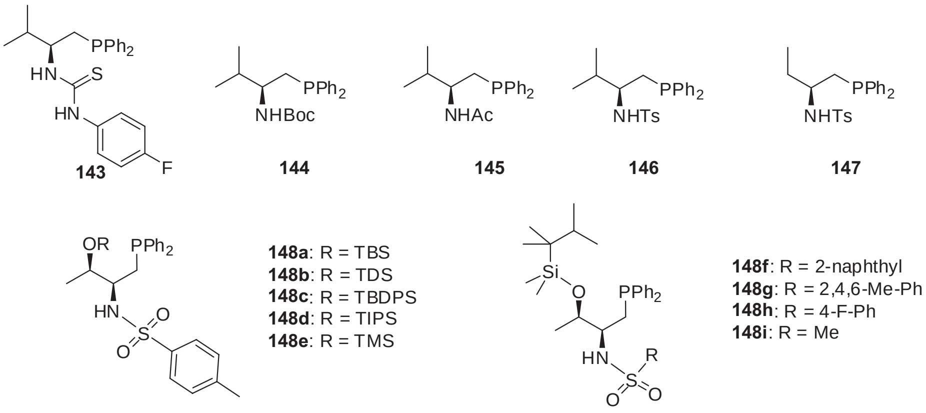
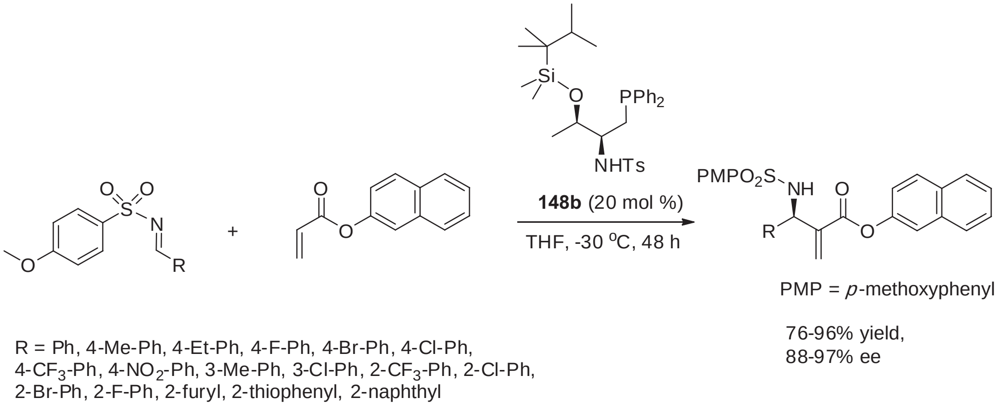


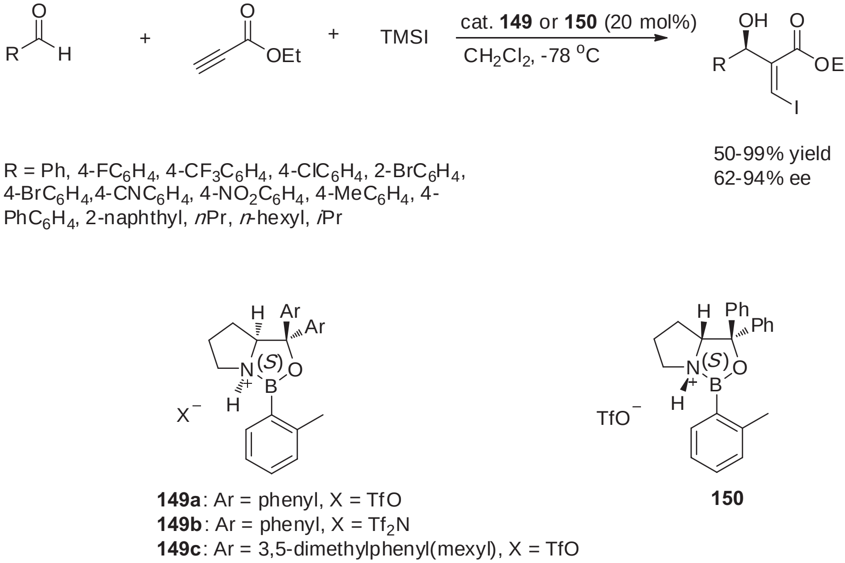
Figure 31.3 Novel bifunctional phosphine-sulfonamide organic catalysts **143**–**148** derived from natural amino acids.


Si
O
PPh2
NHTs
O
O
S
N
R
O
+
O
O
148b (20 mol %)
THF, -30 °C, 48 h
PMPO2S
NH
O
R
O
PMP = p-methoxyphenyl
76-96% yield,
88-97% ee
R = Ph, 4-Me-Ph, 4-Et-Ph, 4-F-Ph, 4-Br-Ph, 4-Cl-Ph,
4-CF3-Ph, 4-NO2-Ph, 3-Me-Ph, 3-Cl-Ph, 2-CF3-Ph, 2-Cl-Ph,
2-Br-Ph, 2-F-Ph, 2-furyl, 2-thiophenyl, 2-naphthyl

Scheme 31.41

31.4.3
Catalytic Asymmetric Induction with Chiral Lewis Acids

Ryu and coworkers reported a highly enantioselective and (*Z*)-stereocontrolled three-component coupling reaction of α,β-acetylenic esters, aldehydes, and trimethylsilyl iodide (TMSI) using chiral cationic oxazaborolidinium catalysts (Scheme 31.42) [54]. Both enantiomers of (*Z*)-β-iodo MBH esters (*R*/*S*) could be obtained enantioselectively by using an (*S*)- or (*R*)-oxazaborolidinium salts (**143** or **144**), which behave as chiral Lewis acids and have been proven to be effective catalysts for Diels–Alder reactions, cyanosilylations, and Michael reactions. These esters can be directly converted into the optically active (*Z*)-β-branched derivatives with retention of configuration. These results are very useful in the synthesis of various optically active (*Z*)-β-branched MBH esters.


R
H
O
+
O
OEt
+
TMSI
cat. 149 or 150 (20 mol%)
CH2Cl2, -78 °C
OH
O
R
OEt
I
50-99% yield
62-94% ee
R = Ph, 4-FC6H4, 4-CF3C6H4, 4-ClC6H4, 2-BrC6H4, 4-BrC6H4, 4-CNC6H4, 4-NO2C6H4, 4-MeC6H4, 4-PhC6H4, 2-naphthyl, nPr, n-hexyl, iPr
H
Ar
Ar
N
(S)
O
B
+
H
X−
H
Ph
Ph
N
(S)
O
B
+
H
TfO−

149a: Ar = phenyl, X = TfO
149b: Ar = phenyl, X = Tf_2N
149c: Ar = 3,5-dimethylphenyl(mexyl), X = TfO

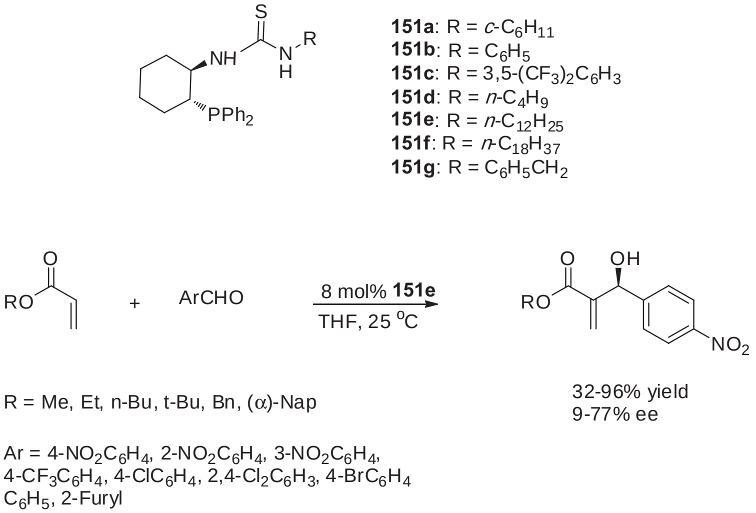
150

Scheme 31.42

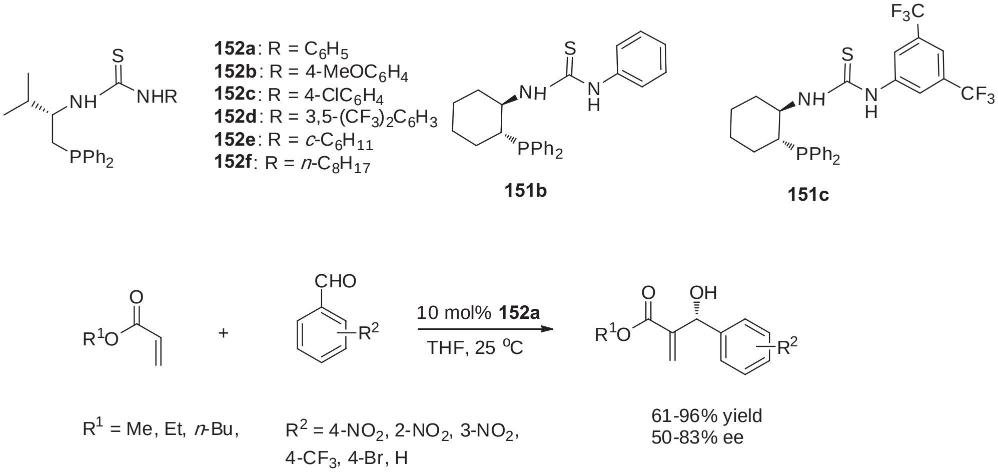
31.4.4
Catalytic Asymmetric Induction with Chiral Brønsted Acids

31.4.4.1 Catalytic Asymmetric Induction with Chiral Thioureas

Recently, Wu and coworkers developed a series of chiral bifunctional phosphine-thioureas that were used as effective organocatalysts in the enantioselective MBH/aza-MBH reactions. They first synthesized a series of chiral bifunctional phosphine-thioureas (Scheme 31.43) and applied them to the enantioselective MBH reaction of aromatic aldehydes with acrylates [55]. It is particularly noteworthy that this new catalytic system is effective for various commercially available acrylates. With 8 mol% of phosphinothiourea **151e**, the MBH reaction could proceed in 5–24 h under mild conditions and afford the desired products in up to 77% ee and moderate-to-excellent yields (up to 96%) (Scheme 31.43). Subsequently, the same authors synthesized a new type of chiral bifunctional phosphine-thiourea, derived from L-valine, that was also efficient for the asymmetric MBH reaction of acrylates with aldehydes [56]. They evaluated these catalysts (**152**, **151b**,**c**, Scheme 31.44) in the asymmetric MBH reaction of 4-nitrobenzaldehyde with methyl acrylate and found that catalyst **152a** was the most efficient. Then, they found that the MBH reactions of various aldehydes with acrylates proceeded smoothly in the presence of 10 mol% **152a**, affording the desired product in moderate-to-excellent

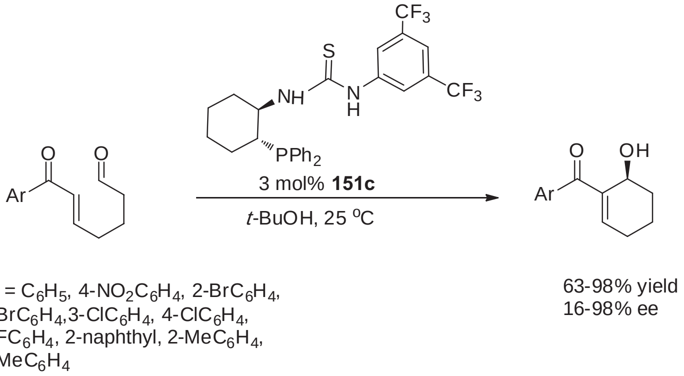

151a: R = c-C_6H_{11}
151b: R = C_6H_5
151c: R = 3,5-$(CF_3)_2C_6H_3$
151d: R = n-C_4H_9
151e: R = n-$C_{12}H_{25}$
151f: R = n-$C_{18}H_{37}$
151g: R = $C_6H_5CH_2$
RO
ArCHO
8 mol% 151e
THF, 25 °C
NO_2
R = Me, Et, n-Bu, t-Bu, Bn, (α)-Nap
32-96% yield
9-77% ee
Ar = 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-BrC_6H_4 C_6H_5, 2-Furyl

Scheme 31.43

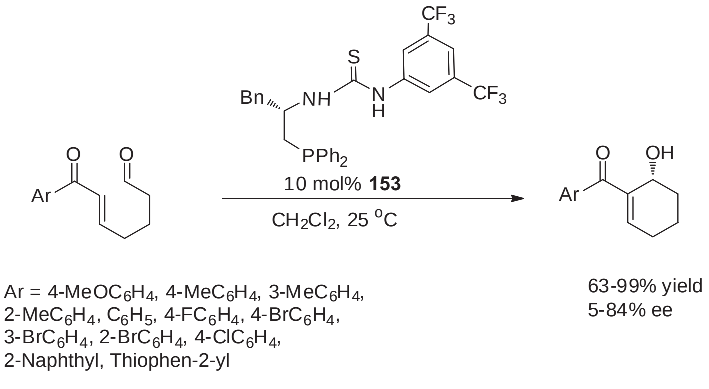


Scheme 31.44

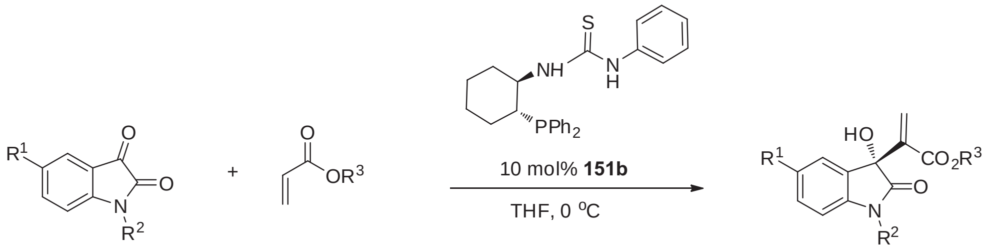
yields with good enantioselectivities of up to 83% ee (Scheme 31.44). Later on, they reported that these chiral cyclohexane-based phosphine-ureas and chiral bifunctional phosphinothioureas derived from L-amino acids were also efficient organocatalysts for the enantioselective intramolecular MBH reactions of ω-formyl-α,β-unsaturated carbonyl compounds [57, 58]. In the presence of 3 mol% of phosphinothiourea **151c** various ω-formyl-enone substrates underwent the enantioselective intramolecular MBH reaction smoothly, giving the desired products in good-to-excellent yields with up to 98% ee under mild reaction conditions (Scheme 31.45). These bifunctional phosphinothioureas (**153**), which were synthesized starting from different amino acids, including L-valine, L-alanine, and L-phenylalanine, could promote the enantioselective intramolecular MBH reactions of ω-formyl-α,β-unsaturated carbonyl compounds, furnishing the cyclic MBH products in up to 84% ee with good to-excellent yields in dichloromethane at room temperature (Scheme 31.46). More recently, they demonstrated that the chiral cyclohexane-based phosphine-ureas were also efficient organocatalysts for the enantioselective MBH reaction of acrylates with isatins [59]. In the presence of 10 mol% of phosphinothiourea **151b**, the MBH reaction of acrylates with isatins could proceed smoothly to afford 3-substituted-3-hydroxyl-oxindole derivatives in excellent yields (82–99%) and moderate enantioselectivities (up to 69% ee) (Scheme 31.47).


CF3
S
NH
N
H
CF3
PPh2
3 mol% **151c**
t-BuOH, 25 °C
O
O
Ar
O
OH
Ar
Ar = C6H5, 4-NO2C6H4, 2-BrC6H4,
3-BrC6H4,3-ClC6H4, 4-ClC6H4,
4-FC6H4, 2-naphthyl, 2-MeC6H4,
3-MeC6H4
63-98% yield
16-98% ee

Scheme 31.45


CF3
S
Bn
NH
N
H
CF3
PPh2
10 mol% **153**
CH2Cl2, 25 °C
O
O
Ar
O
OH
Ar
Ar = 4-MeOC6H4, 4-MeC6H4, 3-MeC6H4,
2-MeC6H4, C6H5, 4-FC6H4, 4-BrC6H4,
3-BrC6H4, 2-BrC6H4, 4-ClC6H4,
2-Naphthyl, Thiophen-2-yl
63-99% yield
5-84% ee

Scheme 31.46

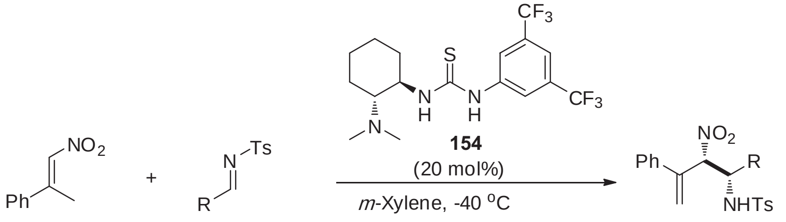


R^1 = H, Me, Cl, H
R^2 = Me, Et, *n*-Bu, Bn, *n*-$C_{12}H_{25}$, H, Me
R^3 = Me, Et, *n*-Bu, *t*-Bu, Bn, Ph, $CH(CF_3)_2$

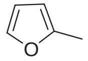
82-99% yield
9-69% ee

Scheme 31.47

In 2009, Xu and coworkers reported the first example of a diastereo- and enantioselective aza-MBH-type reaction accomplished by the asymmetric synthesis of β-nitro-γ-enamines via a (1*R*,2*R*)-diaminocyclohexane thiourea derivative mediated tandem Michael addition and aza-Henry reaction [60]. In the presence of catalyst **154**, various *N*-tosyl imines underwent this reaction smoothly, affording the desired products in good yields (up to 95%) and high enantioselectivities (up to 91% ee) and diastereoselectivities (up to 1 : 99 dr) (Scheme 31.48).



82-95% yield
35:65 - < 1:99 *anti*:*syn*
72-91% ee

R = Ph, 2-MePh, 2-BrPh, 2-FPh, 3-MePh,
4-MePh, 4-BrPh, 4-ClPh, 4-NO_2Ph, 4-CNPh,
4-MeOPh, 3-ClPh, *n*-Pr, 

Scheme 31.48

31.4.4.2 Catalytic Asymmetric Induction with Proline Derivatives

Veselý *et al.* have reported an organocatalytic highly enantioselective aza-MBH reaction of α,β-unsaturated aldehydes with *in situ* generated *N*-Boc and *N*-Cbz imines from the corresponding sulfones under mild and easy conditions [61]. They first screened different catalysts **155a–e** (Figure 31.4), solvents, and base systems to achieve high enantioselectivities, diastereoselectivities, and yields. The (*S*)-proline **155a** with DABCO was identified as the best catalytic system for this reaction

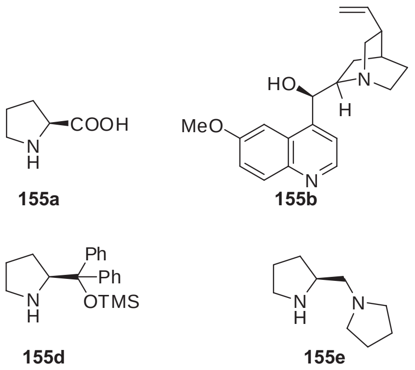
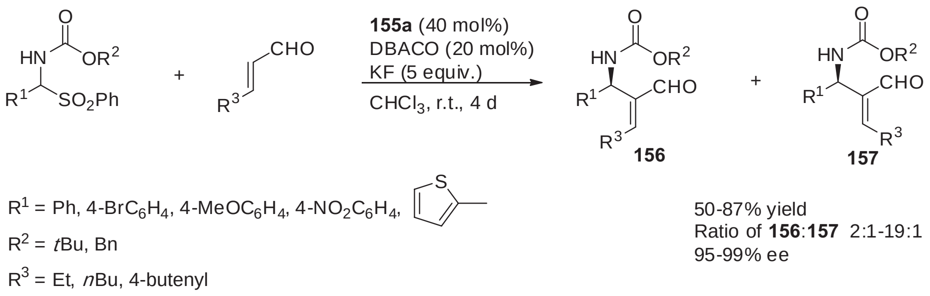


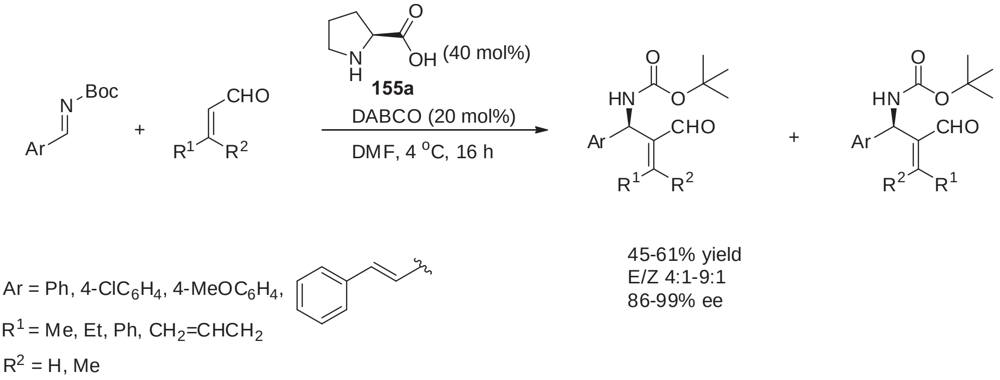
Figure 31.4 Highly enantioselective organocatalysts for the aza-MBH reaction of α,β-unsaturated aldehydes.

and $CHCl_3$ was the best solvent choice. An excess of KF was also added, which was crucial for enhancement of the diastereoselectivity of the reaction. After the optimal reaction conditions were obtained, the authors investigated the reaction scope by using various α-amido sulfones and α,β-unsaturated aldehydes. The reaction tolerated most substrates except aromatic α,β-unsaturated aldehydes such as cinnamic aldehyde, furnishing the desired β-amino carbonyl compounds (**156**) bearing an α-alkylidene group in moderate yields (50–87%), good diastereoselectivity (dr up to 19 : 1), and excellent enantioselectivities (95–99% ee) (Scheme 31.49). More recently, Veselý and Córdova reported a highly enantioselective organo-co-catalytic aza-MBH type reaction between N-carbamate-protected imines and α,β-unsaturated aldehydes [62]. Initially, they screened the co-catalytic systems; the combination of (*S*)-proline and DABCO was identified as the best co-catalytic system for this reaction. After optimization of reaction conditions, they investigated the scope of the catalytic enantioselective addition of enals to *N*-Boc-protected imines. The corresponding β-amino aldehydes were obtained in good yields with high ees (86–99%) (Scheme 31.50). Subsequently, the direct highly



Scheme 31.49

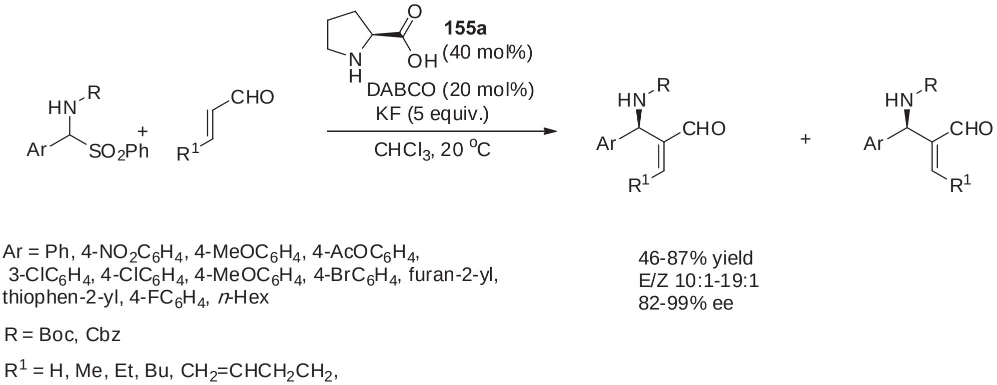
enantioselective addition of α,β-unsaturated aldehydes to bench-stable *N*-carbamate-protected α-amido sulfones was also investigated, giving the corresponding *N*-Boc-and *N*-Cbz-protected β-amino-α-alkylidene aldehydes in good yields with up to 99% ee (Scheme 31.51).



$Ar = Ph, 4-ClC_6H_4, 4-MeOC_6H_4,$
$R^1 = Me, Et, Ph, CH_2=CHCH_2$
$R^2 = H, Me$

45-61% yield
E/Z 4:1-9:1
86-99% ee

Scheme 31.50



$Ar = Ph, 4-NO_2C_6H_4, 4-MeOC_6H_4, 4-AcOC_6H_4,$
$3-ClC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, 4-BrC_6H_4,$ furan-2-yl,
thiophen-2-yl, $4-FC_6H_4$, *n*-Hex

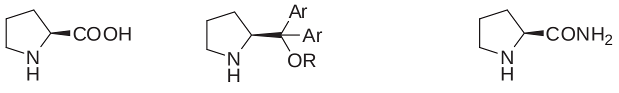
R = Boc, Cbz

$R^1 = H, Me, Et, Bu, CH_2=CHCH_2CH_2,$

46-87% yield
E/Z 10:1-19:1
82-99% ee

Scheme 31.51

In 2010, José Alemán and coworkers reported the first highly enantioselective oxa-Michael/aza-MBH tandem reaction between 2-alkynals and tosylimines leading to optically active 4-amino-4*H*-chromenes using proline derivatives as organocatalysts [63]. A series of proline and its derivatives as shown in Figure 31.5 were screened for this reaction, and the results revealed that **155f** was the best catalyst. To check the scope of the reaction, the authors explored reactions of different aryl, alkyl, and alkenyl alkynals with **158** under the optimized conditions, which were to carry out the reaction catalyzed by 20 or 5 mol% **155f** in the presence of toluene at room temperature (Scheme 31.52). The incorporation of electron-donating groups (*p*-Me, *o*-MeO, and *p*-MeO) at the alkynal's aromatic ring did not

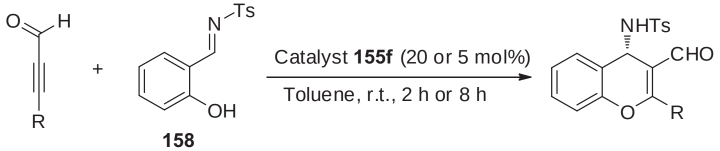


155a

155c: R = H, Ar = Ph
155d: R = TMS, Ar = Ph
155f: R = TMS, Ar = 3,5-$(CF_3)_2$-Ph

155g

Figure 31.5 Proline derivatives used as organocatalysts in the first highly enantioselective oxa-Michael/aza-MBH tandem reaction between 2-alkynals and tosylimines, leading to optically active 4-amino-4*H*-chromenes.



158

R = Ph, *p*-Me-C_6H_4, *o*-MeO-C_6H_4, *p*-MeO-C_6H_4,
3,5-CF_3-C_6H_3, *t*Bu-C_6H_4, *p*-(C_5H_{11})-C_6H_4, *n*-pent,
1-cyclohexenyl,

55-97% yield
94-99% ee

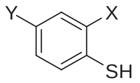
Scheme 31.52

affect the stereoselectivity, with ee's ranging between 94% to 98%. No erosion of yield or stereoselectivity was observed by decreasing the catalytic loading to 5 mol%. Interestingly, electron-withdrawing group at the alkynal's aromatic ring also gave the corresponding product with good enantioselectivity but, however, in low yield (55%). Other alkyl groups at the *para*-position, such as *n*-pent and Bu^t also produced excellent ee's with both 20 and 5 mol% of catalyst. The reactions of alkynals bearing alkyl or alkenyl chains, instead of aryl ones, produced good stereoselectivity and isolated yields.

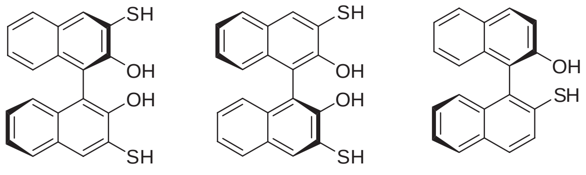
31.4.4.3 **Catalytic Asymmetric Induction with Chiral Thiols**

More recently, Miller and coworkers reported that *ortho*-mercaptobenzoic acid and *ortho*-mercaptophenols **159** could be used as efficient thiol catalysts in both the intramolecular MBH and Rauhut–Currier reaction and they also demonstrated that chiral mercaptophenol afforded the reaction with low to moderate enantioselectivities (Scheme 31.53) [64]. Under established conditions, chiral catalysts (*S*)- and (*R*)-**160** afforded high yields and moderate asymmetric inductions in the MBH reactions. The obtained enantioselectivities remained largely unaffected by the amount of water and base added, catalyst loading, and substrate concentration but were markedly influenced by the reaction temperature. Interestingly, both increasing and decreasing the temperature from the established value of 70 °C resulted in lower ee values. The complete absence of catalytic activity of (*R*)-**161** further emphasizes the crucial importance of a protic substituent at the *ortho*-position to the nucleophilic thiol.

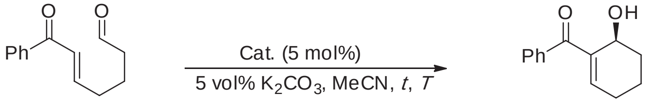
Catalysts



159a X = CO_2H, Y = H
159b X = OH, Y = H
159c X = OH, Y = OH
159d X = H, Y = OH



(*R*)-**160** (*S*)-**160** (*R*)-**161**



Cat.	*t* (h)	*T* (°C)	Yield (%)	ee(%)
(*R*)-**160**	18	20	76	24
(*R*)-**160**	0.5	45	90	35
(*R*)-**160**	0.25	70	89	42
(*S*)-**160**	0.25	70	81	43
(*R*)-**160**	0.1	100	93	34
(*R*)-**161**	16	70	0	-

Scheme 31.53

31.5
Conclusions

During the past few years, different aspects of MBH/aza-MBH reactions, especially asymmetric MBH/aza-MBH reactions, have been studied intensively. In fact, significant developments have been made in the design of new chiral catalysts such as chiral amines, phosphines, and thioureas based on the concept of bi-/multifunctionality for the asymmetric version of the MBH/aza-MBH reaction, and high enantioselectivities have been achieved. Although many important factors governing the reactions were identified, our present understanding of the basic factors, and the control of reactivity and selectivity, remains incomplete. While substrate dependency is still considered to be an important issue, the development of effective catalysts for asymmetric MBH/aza-MBH reactions that are applicable to most of the common activated alkenes and electrophiles still continue to be a challenging endeavor.

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32
Reduction of C=O and C=N

Guilong Li and Jon C. Antilla

32.1
Introduction

The enantioselective hydrogenation of imines and ketones is one of the most important pathways for the preparation of chiral amines and alcohols, which are invaluable building blocks in organic synthesis or exist in natural products, drugs, and agrochemicals [1]. While tremendous success has been achieved for the asymmetric hydrogenation of C=N and C=O with metal catalysis in the past four decades [1d, 2], organocatalytic asymmetric hydride transfer reduction has been emerging as a new promising strategy to reduce C=N and C=O bonds to form optically pure amines and alcohols [3]. Compared to metal catalysis, organocatalysis offers several advantages, for example: (i) organocatalytic reactions are usually performed under mild conditions, such as aerobic conditions; (ii) most organocatalysts are very stable and easy to handle and store; (iii) organocatalysis potentially solves problems of product contamination caused by metal-leaking through metal catalysis. In this chapter, we summarize the recent progress in catalytic asymmetric reduction of C=N and C=O bonds under metal-free reaction conditions according to different types of hydrogen sources. In addition, limited coverage is presented of combination catalysis by organocatalysis and metal catalysis, in which the step leading to a chiral product is catalyzed by a chiral organocatalyst.

32.2
Hantzsch Ester as the Hydride Source

Inspired by the hydride transfer process occurring in biological systems, in which NADH and NADPH are the most common reduction cofactors (Figure 32.1), organic chemists have been pursuing routes to mimic this process in organic synthesis. Among all the hydride donors utilized in organic synthesis, 1,4-dihydropyridine (**1**, Figure 32.1), also known as the Hantzsch ester (HEH), is the most similar analog of those reduction cofactors, in terms of chemical reactivity and structural

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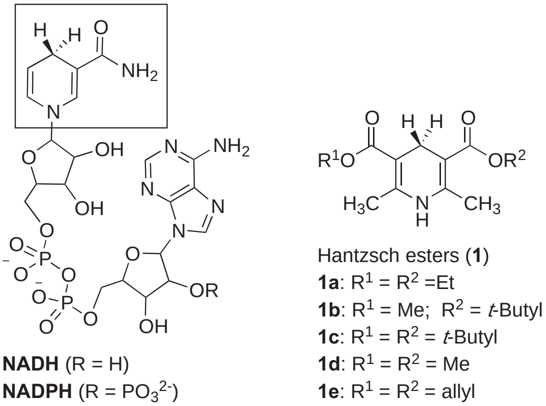


NADH (R = H)
NADPH (R = PO_3^{2-})

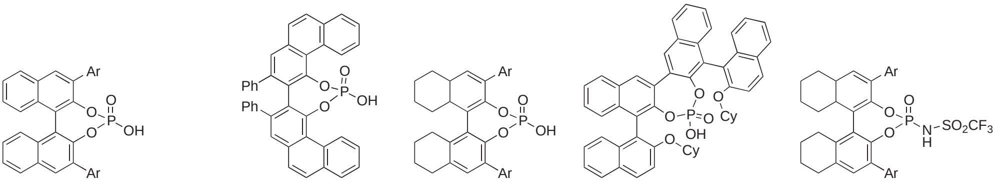
Hantzsch esters (**1**)
1a: $R^1 = R^2$ =Et
1b: R^1 = Me; R^2 = *t*-Butyl
1c: $R^1 = R^2$ = *t*-Butyl
1d: $R^1 = R^2$ = Me
1e: $R^1 = R^2$ = allyl

Figure 32.1 The most common reduction cofactors in nature, NADH and NADPH, and Hantzsch esters (HEH), the most similar analog of the reduction cofactors, in terms of chemical reactivity and structural functionalities.

functionalities (Figure 32.1). In fact, HEH has been utilized as a biomimetic hydride source for reduction chemistry since its first application for reducing methylene blue as early as 1936 by Karrer and Benz [4]. Since there are already many excellent reviews of reduction chemistry by HEH [3b, 3d, 5], in this chapter we will only focus on the asymmetric organocatalytic reduction of C=N and C=O bonds with HEH as the hydride donor.

32.2.1
Reduction of C=N Bonds in Acyclic Systems

In 1989, Singh and Batra reported the first example of imine reduction catalyzed by salts of Brønsted acids and α-amino acids with Hantzsch esters **1a** as the reducing agent [6]. The best ee was 65%; however, this work was ignored until 2004, when List *et al.* reported the first metal-free, organocatalytic enantioselective hydrogen transfer reduction of α,β-unsaturated aldehydes [7]. This work launched a new wave of research interest in organocatalytic reduction. The preparation of chiral amines still represents one of the greatest challenges in organic synthesis. Soon after this, Rueping's group discovered that *N*-aryl ketimines (**14**) could be reduced under mild conditions with Hantzsch ester **1a** as the hydride donor and chiral phosphoric acid (**2**, Figure 32.2) as the catalyst [8]. In this report, they screened several chiral phosphoric acids and solvents to establish the optimized reaction conditions. Although most of results, including yields and enantioselectivities, were moderate and the catalyst loading was as high as 20 mol%, this report is the first successful chiral phosphoric catalyzed transfer hydrogenation of imines (Scheme 32.1).



2: Ar = 3,5-(CF_3)-phenyl
3: Ar = 2,4,6-(triisopropyl)-phenyl
4: Ar = Ph_3Si
6: Ar = 9-anthryl
7: Ar = 9-phenanthryl
8: Ar =2-naphthyl
13: Ar =2-MeC_6H_4

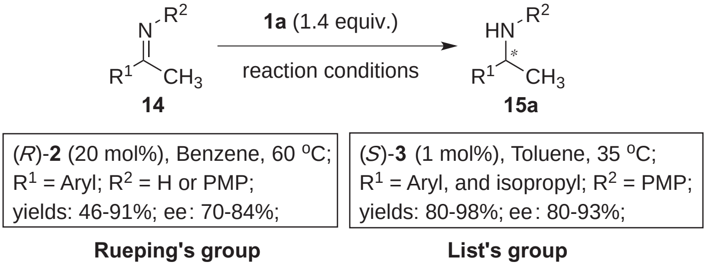
5: VAPOL-PA

9: Ar = Ph_3Si
12: Ar = Ph

10

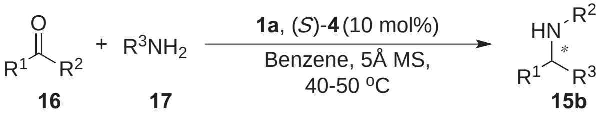
11: Ar = 2-naphthyl

Figure 32.2 Chiral phosphoric acids used as organocatalysts.


14
1a (1.4 equiv.)
reaction conditions
15a
(R)-2 (20 mol%), Benzene, 60 °C;
R1 = Aryl; R2 = H or PMP;
yields: 46-91%; ee: 70-84%;
Rueping's group
(S)-3 (1 mol%), Toluene, 35 °C;
R1 = Aryl, and isopropyl; R2 = PMP;
yields: 80-98%; ee: 80-93%;
List's group

Scheme 32.1

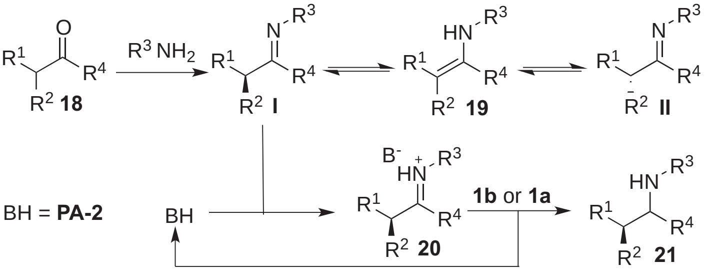
List's group and MacMillan's group soon reported further advancements, independently. List *et al.* showed that the same reduction could be significantly improved in terms of yields and enantioselectivities by using a new sterically congested chiral phosphoric acid, namely, TRIP (**3**) [9]. Furthermore, the catalyst loading could be as low as 1 mol% and the ketimine **14** could form *in situ*, before the reduction was performed. Notably, aliphatic ketimines were potentially suitable substrates for this asymmetric transfer hydrogenation, although the authors provided only one case, which was derived from 3-methyl-2-butanone (Scheme 32.1). Independently and at the same time, MacMillan *et al.* published their elegant results on the asymmetric reductive amination catalyzed by phosphoric acid **4** [10]. In the presence of molecular sieves, the ketimines generated *in situ* are reduced to chiral amines with high to excellent enantioselectivities. The reductive amination is quite general for various ketones **16** and aromatic amines **17.** However, R^3 is still limited to a methyl group in order to obtain good ee values. Computational studies revealed that while a methyl group (R^3) leaves the C=N *Si*-face exposed to hydride addition, the terminal CH_3 of the ethyl leads to shielding of both enantiofacial sites of the C=N bond (Scheme 32.2).



yields: 80-98%; ee: 80-93%
R^1 = Aryl, and aliphatic group;
R^2 = Aryl and heteroaromatic group;
R^3 = CH_3, CH_2F, etc.

Scheme 32.2

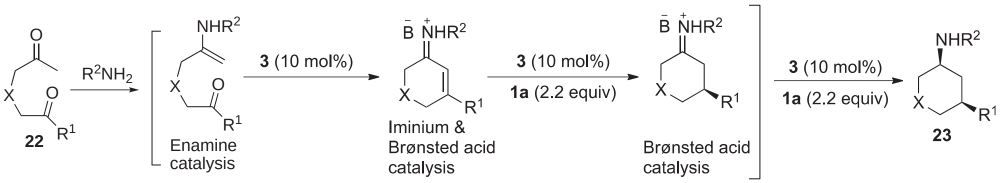
While the previous mentioned hydride transfer processes of ketones provides chiral α-branched amines, List *et al.* conceived that chiral β-branched amines **21** could be synthesized by reductive amination of α-branched aldehydes **18** ($R^4 = H$) via an enantiomer-differentiating kinetic resolution [Scheme 32.3 (I)] [11]. Indeed, after screening various phosphoric acid catalysts and Hantzsch esters, **3** was found to be an efficient catalyst for differentiating the imine enantiomers and imine I is reduced much faster than the other enantiomer (II), which is racemized to I during the process, thus affording the corresponding chiral β-branched amines **21** in moderate to excellent yield and ee. This methodology is quite general when R^1 is an aromatic group, while aliphatic R^1 gives relatively lower ee's and yields. This idea was successfully extended to α-branched ketones in 2010 (Scheme 32.3) [12]. Enantioselectivities of up to 96% ee's were obtained for the synthesis of various valuable *cis*-2-substituted cyclohexylamines, which are found as intermediates in pharmaceuticals. During the course of developing asymmetric reductive aminations, the List group also discovered an elegant cascade reaction with the combination of enamine catalysis, iminium and Brønsted acid catalysis (Scheme 32.4). This reaction sequence gives rise to *cis*-3-substituted (hetero)cyclohexylamines **23** from 2,5-diones **22** with excellent ee and diastereoselectivities up to 99 : 1 [13].



(I) **1b**; α-substituted aldehydes: R^1 = aryl or alkyl; R^2 = Me, Et; R^3 = PMP, 4-$CF_3C_6H_4$; R^4 = H; yields: 39-96%, ee: 40-98%.

(II). **1a**; α-substituted ketones: most substrates are α-substituted cyclohexanones, R_1 = alkyl, aryl, alkenyl, etc; yields: 63-92%; ee: 86-96%.

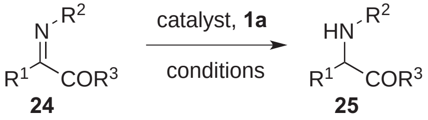
Scheme 32.3



R^1 = alkyl, β-naphthyl; R^2 = PEP, PMP; X = CH_2, O, S; yields: 35-89%; *ee*: 82-96%; *dr*: 2:1 to 99:1.

Scheme 32.4

Chiral α-amino acids are one of the most important organic molecules existing in living systems; thus developing general methodologies for the synthesis of chiral α-amino acid derivatives in high levels of enantioselectivity is of considerable importance. Inspired by the chiral phosphoric acid catalyzed imine reductions by Rueping, List, and MacMillan, Antilla *et al.* developed a highly enantioselective reduction of α-imino esters (Scheme 32.5) [14]. Using 5 mol% of VAPOL derived phosphoric acid as the catalyst, the asymmetric reduction of various aromatic α-imino esters **24** led to excellent enantioselectivities (up to 99%) and yields with Hantzsch ester **1a** as the hydride donor. With molecular sieves as the desiccant, aliphatic α-imino esters also afforded excellent ee, although yields are slightly low because α-imino esters are generated *in situ* to avoid possible side reactions. Very shortly after Antilla's publication, You *et al.* independently reported the same reduction chemistry (Scheme 32.5) [15]. Using **6** as the catalyst, the transfer hydrogenation of α-imino esters **24** provides excellent ee (up to 98%). Most examples were limited to aromatic substrates. When they employed β,γ-alkynyl α-imino esters for the asymmetric transfer hydrogenation they found that both the alkyne and imine functionalities could be reduced to afford chiral *trans*-alkenyl α-imino esters in very high enantioselectivities (up to 96%), even though yields are moderate or low. Further experiments showed that the reduction of the carbon–carbon triple bond is faster than that of the C=N double bond [16].



5 (5 mol%), **1a** (1.4 equiv.),toluene, 50°C; R^1 = aryl, linear alkyl; R^2 = PMP or Ph; R^3 = OEt, OMe; yields: 85-98%; ee: 94-99%

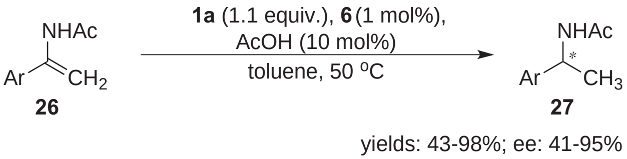
Antilla's group

6 (1 mol%), **1a** (1.4 equiv.), Et_2O, rt; R^1 = aryl, Cy; R^2 = PMP; R^3 = OEt, OMe, OBn and O*i*-Pr, NH*t*-Bu; yields: 46-95%; ee: 33-98%

You's group

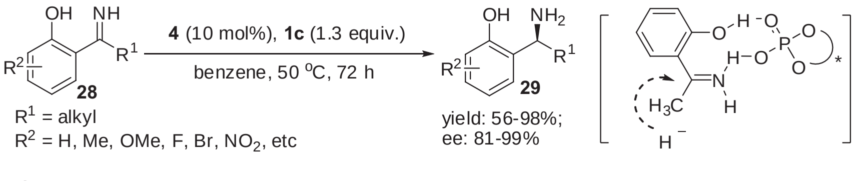
Scheme 32.5

While most chiral phosphoric acid-catalyzed hydride transfer reductions of imines are limited to substrates derived from aniline and its analogues, leading to relatively harsh reaction conditions for the deprotection to afford a free amino group, the hydrogenation of an imine with an easily removable protective group would be highly desirable. *N*-Acyl enamides are popular substrates for preparing chiral amines via asymmetric hydrogenation, partially due to the ease of removal of the *N*-acyl group. Antilla and Li found *N*-acyl enamides **26** could be efficiently reduced by Hantzsch ester **1a** in the presence of catalyst **6** to give chiral amides **27**, with up to 95% ee (Scheme 32.6) [17]. The catalyst loading could be as low as 1 mol%, utilizing acetic acid (10 mol%) as a co-catalyst. The acetic acid is believed to generate the iminium intermediate, thus helping to decrease the chiral catalyst loading. Recently, List *et al.* reported preliminary results of the reductive amination of ketones with benzylamine [18]. The reduction is performed under refluxing conditions at reduced pressure (57 °C, 167 mbar) for 5 days, while the benzyl protective group is readily removed to provide chiral amines with 46–88% ee.



Scheme 32.6

An interesting discovery by Wang *et al.* demonstrated that unprotected ketimines **28**, derived from *ortho*-hydroxyaryl alkyl ketones, could be reduced in high to excellent enantioselectivities with Hantzsch ester **1c** as the hydride donor (Scheme 32.7) [19]. The *ortho*-hydroxy group is proposed to form a hydrogen bond with **4**, thus leaving the *Re*-face open to hydride attach. This strategy was successfully extended to the asymmetric hydrogenation of diarylketimines by the same group, with the same catalyst (80–91% ee). However, an *N*-aryl protective group is necessary for ketimine substrates in the transfer hydrogenation [20].

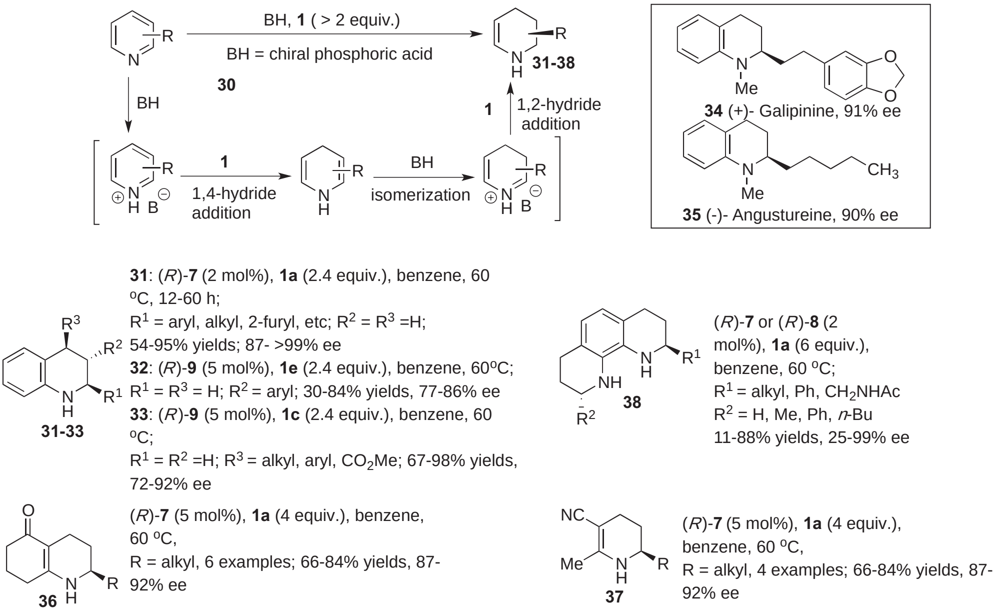


Scheme 32.7

32.2.2
Reduction of C=N Bonds in Cyclic Substrates

32.2.2.1 Reduction of C=N Bonds in Heteroarenes

The asymmetric reduction of C=N bonds in cyclic organic compounds represents one of the most important methodologies for preparing nitrogen-containing heterocycles, which extensively exist in numerous natural products, particularly alkaloids. Rueping *et al.* pioneered the chiral phosphoric acid-catalyzed reduction of C=N bonds in heteroarenes. They successfully extended their transfer hydrogenation from imines to quinolines (Scheme 32.8) [21]. 1,2,3,4-Tetrahydroquinolines are not only important compounds for pharmaceuticals and agrochemicals, but also they are key core structures in many natural products. Using more than two equivalents Hantzsch ester **1a** as the hydride donor, and **7** as the catalyst, various 2-substituted quinoline derivatives could be reduced to afford optically active tetrahydroquinolines (**31**) in high to excellent enantioselectivities through a cascade sequence reaction (1,4-hydride addition, isomerization, and 1,2-hydride addition). With this elegant methodology, several tetrahydroquinoline alkaloids, such as (+)-galipinine (**34**) and (–)-angustureine (**35**) were efficiently synthesized with up to 91% ee. Subsequent studies demonstrated that various quinolines bearing different substituted groups on the 3 and 4-site were suitable for the asymmetric transfer hydrogenation. With H_8-BINOL derived phosphoric acid **9** as the catalyst, chiral tetrahydroquinolines **32** [22] and **33** [23] were obtained in high ee. The



31: (*R*)-**7** (2 mol%), **1a** (2.4 equiv.), benzene, 60 °C, 12-60 h;
R^1 = aryl, alkyl, 2-furyl, etc; R^2 = R^3 =H;
54-95% yields; 87- >99% ee
32: (*R*)-**9** (5 mol%), **1e** (2.4 equiv.), benzene, 60°C;
R^1 = R^3 = H; R^2 = aryl; 30-84% yields, 77-86% ee
33: (*R*)-**9** (5 mol%), **1c** (2.4 equiv.), benzene, 60 °C;
R^1 = R^2 =H; R^3 = alkyl, aryl, CO_2Me; 67-98% yields, 72-92% ee

(*R*)-**7** or (*R*)-**8** (2 mol%), **1a** (6 equiv.), benzene, 60 °C;
R^1 = alkyl, Ph, CH_2NHAc
R^2 = H, Me, Ph, *n*-Bu
11-88% yields, 25-99% ee

(*R*)-**7** (5 mol%), **1a** (4 equiv.), benzene, 60 °C,
R = alkyl, 6 examples; 66-84% yields, 87-92% ee

(*R*)-**7** (5 mol%), **1a** (4 equiv.), benzene, 60 °C,
R = alkyl, 4 examples; 66-84% yields, 87-92% ee

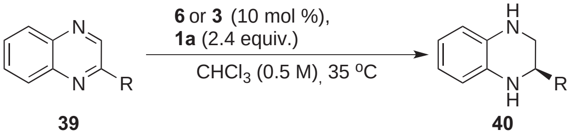
Scheme 32.8

successful catalysts were not only limited to **7** and **9.** Du *et al.* developed a novel double axially chiral phosphoric acid (*R,R*)-**10,** which was found to be even more efficient than those catalytic systems reported by Rueping *et al.* The catalyst loading can be as low as 0.2 mol% and most yields were as high as 99%. The enantioselectivities range from 86% to 98% [24].

In addition to quinolines, pyridines were also found to be suitable substrates for this cascade reduction. Chiral tetrahydropyridines **36** and **37** were synthesized with up to 92% ee by employing (*R*)-**7** as the catalyst [25]. Phenanthroline, which has the same functional group as quinoline and pyridine, was reported by Metallinos *et al.* to undergo transfer hydrogenation to the corresponding octahydrophenanthroline **38** with up to 99% ee, whereas most other substrates provided moderate ee [26].

Interestingly, while the above-mentioned transfer hydrogenation reactions catalyzed by chiral Brønsted acids were usually performed under strictly anhydrous conditions, Rueping and Theissmann reported that this kind of catalysis could be conducted in pure aqueous conditions [27]. After extensive studies on optimizing the reaction conditions, they found that by using brine as the reaction media, 2 mol% **3** as the catalyst, and Hantzsch ester **1c** as the hydride source various 2-arylsubstituted quinoline derivatives are reduced to the corresponding chiral tetrahydroquinolines with high to excellent enantioselectivities and yields. The authors believe that the good stereoselectivity obtained in the aqueous solution is induced by the large isopropyl substituents of **3,** which is able to form a hydrophobic pocket to encase the substrate.

Tetrahydroquinoxalines are biologically and pharmacologically important compounds. Generally, chiral tetrahydroquinoxalines are synthesized in multiple steps from chiral amino alcohols or amino acids. Rueping *et al.* developed a general, catalytic asymmetric transfer hydrogenation of quinoxalines **39** for the preparation of chiral tetrahydroquinoxalines **40** (Scheme 32.9) [28]. Interestingly, the reactivity was determined by the concentration of the solvent. A higher concentration results in a faster reaction.



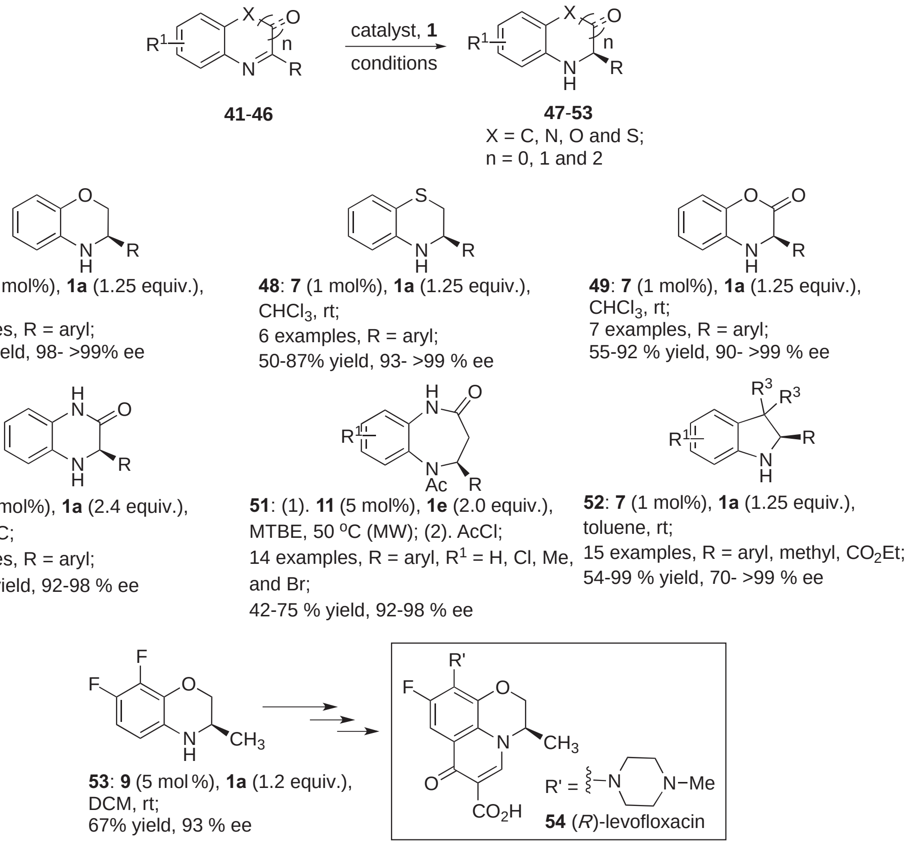
14 examples, R = aryl;
73-98 % yield, 80-98 % ee

Scheme 32.9

32.2.2.2 **Reduction of Cyclic Imines**

During the study on enantioselective organocatalytic reductive amination, MacMillan *et al.* found that the pyruvic acid-derived cyclic imino ester could be efficiently reduced to yield the corresponding alanine amino ester with 97% ee and 82% yield

[10]. Rueping *et al*. conducted systematic studies on the asymmetric transfer hydrogenation of cyclic imines. They investigated the reduction of cyclic imines of different ring-size, including six, seven, and five-membered rings (**41–46,** Scheme 32.10). Chiral dihydro-2*H*-benzoxazines **47**, dihydro-2*H*-benzothiazines **48** [29], dihydro-2*H*-benzoxazinones **49,** dihyroquinoxalinones **50** [28], dihydrobenzodiazepinones **51** [30], and indulines **52** [31] are synthesized by means of a hydride transfer reaction utilizing the corresponding chiral phosphoric acids as catalysts and HEH (**1a–1e**) as the hydride donor. They found that benzoxazines **41** could be reduced to afford optically pure dihydro-2*H*-benzoxazines **47** with a notably low catalyst loading of **7** (as low as 0.01 mol%) with only a slight decrease in the enantioselectivity (about 3–6% loss of ee). Benzothiazines **42,** which are usually toxic for transition metal catalysts, due to sulfur forming a stable complex with metal catalysts, are also suitable substrates for this catalytic system, providing chiral dihydro-2*H*-benzothiazines **48** with excellent enantioselectivities. However,



X = C, N, O and S;
n = 0, 1 and 2

47: **7** (0.1 mol%), **1a** (1.25 equiv.), $CHCl_3$, rt;
6 examples, R = aryl;
92-95% yield, 98- >99% ee

48: **7** (1 mol%), **1a** (1.25 equiv.), $CHCl_3$, rt;
6 examples, R = aryl;
50-87% yield, 93- >99 % ee

49: **7** (1 mol%), **1a** (1.25 equiv.), $CHCl_3$, rt;
7 examples, R = aryl;
55-92 % yield, 90- >99 % ee

50: **6** (10 mol%), **1a** (2.4 equiv.), THF, 50 °C;
5 examples, R = aryl;
42-75 % yield, 92-98 % ee

51: (1). **11** (5 mol%), **1e** (2.0 equiv.), MTBE, 50 °C (MW); (2). AcCl;
14 examples, R = aryl, R^1 = H, Cl, Me, and Br;
42-75 % yield, 92-98 % ee

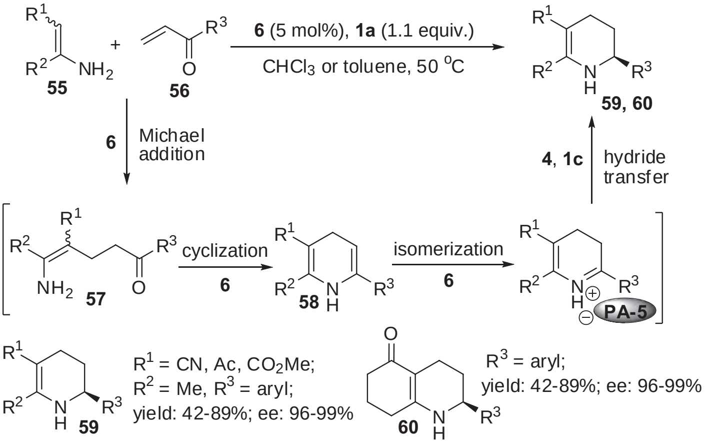
52: **7** (1 mol%), **1a** (1.25 equiv.), toluene, rt;
15 examples, R = aryl, methyl, CO_2Et;
54-99 % yield, 70- >99 % ee

53: **9** (5 mol %), **1a** (1.2 equiv.), DCM, rt;
67% yield, 93 % ee

Scheme 32.10

yields were lower than for the reduction of **47.** Cyclic iminoesters and cyclic iminoamides could also be reduced to the corresponding dihydro-2*H*-benzoxazinones **49** and dihyroquinoxalinones **50** in the presence of **7** or **6.** In this study, Rueping *et al.* propose an activation model where the cyclic imine forms a chiral ion pair with the chiral phosphoric acid and, thus, the hydride nucleophile attacks the π bond from the less hindered *Si* face to afford the corresponding chiral amines. This proposal was supported by an X-ray structure of catalyst **7** and the aryl glycine [28]. In addition to six-membered ring cyclic imines, Rueping *et al.* also recently reported the asymmetric reduction of 4-substituted-1*H*-[1, 5]benzodiazepine-2(3*H*)-ones **45,** which are seven-membered ring cyclic imines. In this reduction, phosphoric acids were not strong enough to catalyze the hydride transfer reaction; however, a stronger acid, *N*-triflyl phosphoramide, **11** was disclosed to be the choice for this reduction under microwave irradiation [30]. Various dihydrobenzodiazepinones **51** are prepared with very high enantioselectivities after acylation of the amine products. The organocatalytic reduction of 3*H*-indole **46,** a five-membered cyclic imine, was also conducted by Rueping *et al.* recently [31]. This reduction is catalyzed by **7** under very mild reaction conditions and 96% to ≥99% ee was obtained when the 3*H*-indole bears an aryl group at the 2-position; however, only moderate ee was obtained for 2-alkyl-substituted 3*H*-indoles. Finally, the value of the organocatalytic asymmetric transfer hydrogenation is demonstrated by the synthesis of fluoroquinolones, which are utilized as key building blocks for preparing drugs like (*R*)-levofloxacin (**54**) and (*R*)-flumequine [32].

After great success in the reduction of imines, quinolines, and pyridines, Rueping *et al.* designed a chiral phosphoric acid-catalyzed cascade reaction, in which enamines and enones are heated with Hantzsch ester **1a** and (*R*)**-6,** then a Michael addition, cyclization, isomerization and hydride transfer reaction take place successively to afford chiral tetrahydropyridine **59** and azadecalinone **60** products in excellent enantioselectivities (Scheme 32.11) [33]. Remarkably,



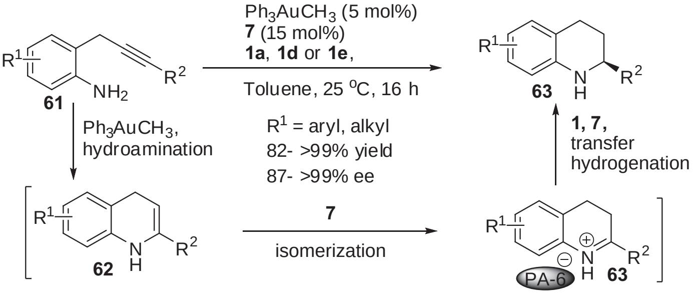
Scheme 32.11

this cascade reaction starts from three simple reactants and combines several Brønsted acid-catalyzed steps in one pot to synthesize complex molecules in high enantiopurity.

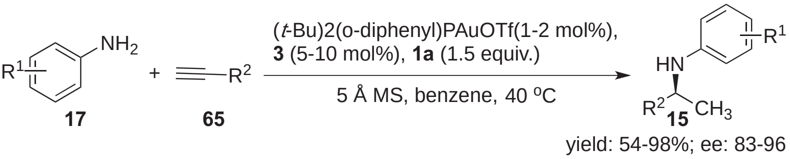
32.2.3
Transfer Hydrogenation Combined with Other Transformations

The combination of organocatalysis and metal catalysis in one pot provides high efficiency in organic synthesis [34]. Combination catalysis usually leads to a cascade reaction, in which each step is catalyzed by a certain catalyst, either an organocatalyst or a metal catalyst. The key to designing such catalysis is that both the metal catalyst and organocatalyst should tolerate each other when they catalyze different types of reactions.

In 2009, Gong *et al.* reported a relay catalysis, in which they proposed an achiral gold complex as catalyzing an intramolecular hydroamination to produce a 1,4-dihydroquinoline **62,** which is then relayed by a chiral Brønsted acid catalyzed asymmetric transfer hydrogenation to yield optically active tetrahydroquinolines **64** in high to excellent enantioselectivities (Scheme 32.12). Experiments show that the gold catalyst has very little effect on the transfer hydrogenation step, which is almost fully controlled by **7** [35]. Che and Liu *et al.* reported, shortly after Gong, a similar strategy using a gold(I) complex, but with *in situ* generated acyclic imines, followed by an asymmetric hydride transfer reaction catalyzed by **3** (similar with List's work), to synthesize chiral amines **15** in high to excellent enantioselectivities (Scheme 32.13) [36].

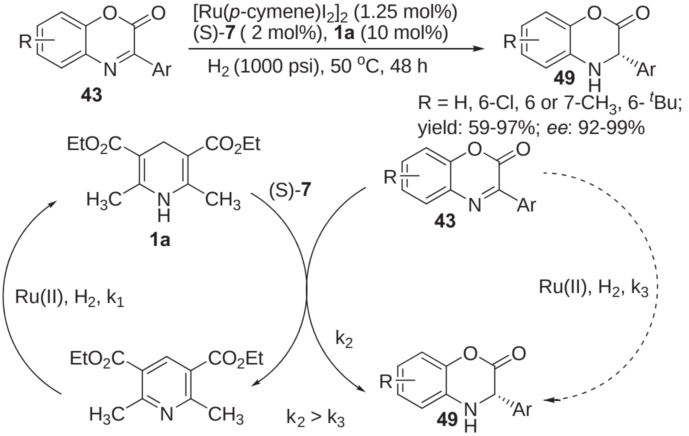


Scheme 32.12



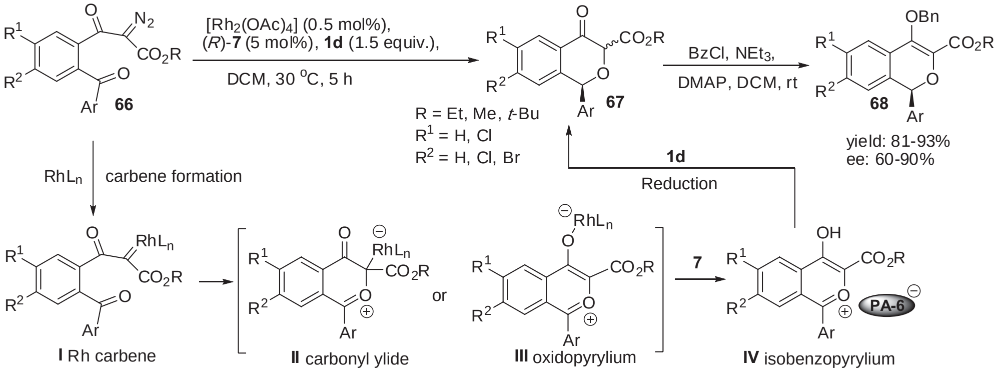
Scheme 32.13

Although the Hantzsch ester has been successfully utilized as a hydride donor in asymmetric hydrogenation, it is not an atom economic reagent for organic synthesis, since only one hydride is transferred to the product, whereas the other portion generates one equivalent of pyridine byproduct **1a′**. As a potential resolution for this issue, Zhou *et al.* recently developed a catalytic combination that enables transfer hydrogenation using only catalytic amounts of Hantzsch ester, rather than more than stoichiometric amounts (Scheme 32.14). The key for this relay catalysis is that the Ru(II) complex selectively catalyzes the hydrogenation of pyridine **1a′** to recover hydride donor **1a** (k_1), while it has very small potency in reducing benzoxazinone **43** to form dihydrobenzoxazinone **49** (k_3) [37].


[Ru(p-cymene)I2]2 (1.25 mol%)
(S)-7 (2 mol%), 1a (10 mol%)
H2 (1000 psi), 50 °C, 48 h
43
49
R = H, 6-Cl, 6 or 7-CH3, 6- tBu;
yield: 59-97%; ee: 92-99%
1a
(S)-7
Ru(II), H2, k1
Ru(II), H2, k3
k2
k2 > k3

Scheme 32.14

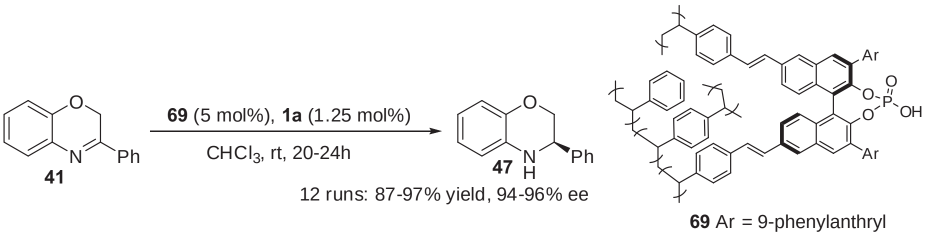
A successful asymmetric organocatalytic based C=O reduction with the Hantzsch ester was not reported until very recently. Terada and Toda developed a relay catalysis that combined Rh(II) and a chiral phosphoric acid catalyst in a one-pot reaction (Scheme 32.15). In this reaction sequence, a rhodium carbene (I) forms in the first step and is followed with an intramolecular cyclization to afford carbonyl ylide intermediate II or oxidopyrylium III. These intermediates are protonated by **7** to yield the chiral ion pair between isobenzopyrylium and the conjugate base of **7** (IV). Intermediate IV is further reduced *in situ* by Hantzsch ester **1d** to produce the isochroman-4-one derivative **67**, which is finally trapped with benzoyl chloride to afford the chiral product **68**. Surprisingly, the reaction sequence proceeds well to give racemic product even without the addition of chiral **7**, while giving rise to the desired product with high enantioselectivity in the presence of chiral Brønsted acid **7** [38].



Scheme 32.15

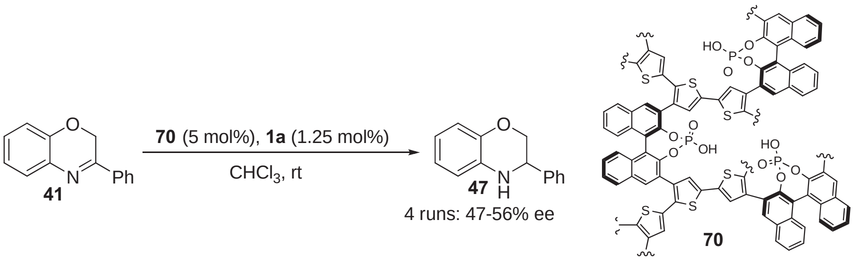
32.2.4
Immobilized Chiral Catalysts for C=N Bond Reduction [39]

BINOL-derived phosphoric acids have proven to be versatile and powerful catalysts for various organic transformations. Usually, to obtain high enantioselectivities, suitable substituents at the 3,3′-positions of the BINOL backbone are necessary. Since several steps are required to prepare such catalysts, the development of recoverable chiral phosphoric acids would be highly desirable. In 2010 [40] Rueping *et al.* prepared copolymer catalyst **69**, in which **7** is immobilized (Scheme 32.16). The effect of **69** has been tested in the asymmetric reduction of benzoxazine **41** with Hantzsch ester **1a** and was found to be highly efficient even after 12 runs. The recovery of **69** is quite easy and simple filtration is needed since the reaction is heterogeneous.



Scheme 32.16

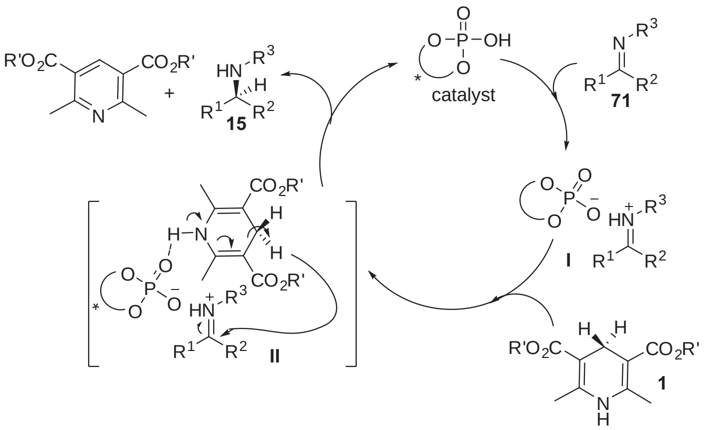
Recently, Schmidt *et al.* reported the novel microporous polymer network **70**, which was prepared via oxidative coupling of 3,3′-dithienyl BINOL derived phosphoric acid (Scheme 32.17). This interesting chiral polymer shows good activity for the asymmetric hydrogenation of benzoxazine **41**, even after reuse four times (ee 47%–56%) [39].



Scheme 32.17

32.2.5
Mechanistic Consideration

While, there is no clear mechanism for the chiral phosphoric acid catalyzed transfer hydrogenation of imines with Hantzsch esters as the hydride donor, it is generally believed that the imine is activated by the chiral acid via formation of an ion pair. This chiral ion pair provides a chiral environment that exposes the *Re* or *Si* face for the nucleophilic attack of hydride. This proposal is supported by a crystal structure of the iminium (I, Scheme 32.18) produced from the chiral acid and imine [8, 10]. Detailed theoretical studies using DFT methods have been performed by Goodman and Simon [41] and Himo *et al.* [42] independently. Both studies reveal that the chiral phosphoric acid not only functions as a Brønsted acid to activate the imine by forming an iminium but also functions as a Lewis base to coordinate the HEH via a hydrogen-bond (II, Scheme 32.18). Meanwhile, the absolute configuration of the amine products could also be explained according to the "three-point contact model" proposed by Goodman *et al.*



Scheme 32.18

32.3
Trichlorosilane as the Reducing Reagent

Compared with the chiral Brønsted acid catalyzed asymmetric transfer hydrogenation, in which the electrophilic substrate (C=N or C=O bond) was activated by a Brønsted acid via formation of an ion pair or hydrogen bond, Lewis base catalyzed hydrosilylation of C=N or C=O bonds proceeds through a coordination of the Lewis base with a silane, which could form a more reactive hypervalent silicate complex [43]. In 1997, Kagan and Schiffers reported the first asymmetric reduction of carbonyl compounds with trimethoxysilane catalyzed by a monolithium salt of (*R*)-BINOL, which functions as a Lewis base to activate trimethoxysilane [44]. In the past decade, asymmetric organocatalysis has witnessed significant advances. Silanes are very attractive reagents since they are relatively cheap, non-toxic, and are considered non-metal compounds – thus they have received considerable attention from organic chemists. Trichlorosilane, due to the strong electron-withdrawing effect of the three chlorine atoms, exhibits enhanced Lewis acidity and, thus, could be easily activated by the corresponding Lewis base catalysts to deliver hydride. In 1999, Matsumura *et al*. reported the first organocatalytic asymmetric reduction of ketones using Cl_3SiH as the hydride donor [45]. This work sets a milestone for the chiral Lewis base catalyzed hydrosilation of C=N and C=O bonds. In this chapter, we summarize important progress in this topic in chronological order. In addition, all the Lewis base catalysts are listed in chronological order in Figure 32.3.

32.3.1
Asymmetric Reduction of Ketimines

In 2001, Matsumura *et al*. reported the first asymmetric reduction of ketimines **71** by using trichlorosilane as the hydride donor and chiral *N*-formylpyrrolidine derivatives (**71**, **72**) (Figure 32.3), which are derived from L-proline, as Lewis base catalysts [46]. Although moderate enantioselectivities for chiral amine products (49–66% ee) are obtained, this preliminarily result opened the door to the chemistry of reducing imines with organic Lewis base catalysts (entry 1, Table 32.1). Three years later, Malkov and Kocovsky *et al*. developed another type of *N*-formyl based Lewis base derived from L-valine (**74**) (entry 2, Table 32.1) [47]. These types of catalysts are more flexible since they are open chain, compared with the cyclic proline framework of **72**, yet they are highly efficient for the asymmetric reduction and provided up to 92% ee. The authors propose a transition state, where **74** coordinates with trichlorosilane to form a hexacoordinated complex, in which hydrogen bonding and π–π stacking are possibly involved according to experiments they conducted (Figure 32.4).

While an *N*-formyl group is essential for previous chiral activators of trichlorosilane, Kocovsky *et al*. and Matsumura *et al*. independently reported new non-*N*-formyl Lewis base organocatalysts in 2006 (entry 3, Table 32.1). After exploring various chiral pyridyl-oxazolines and isoquinolyloxazolines, Kocovsky *et al*.

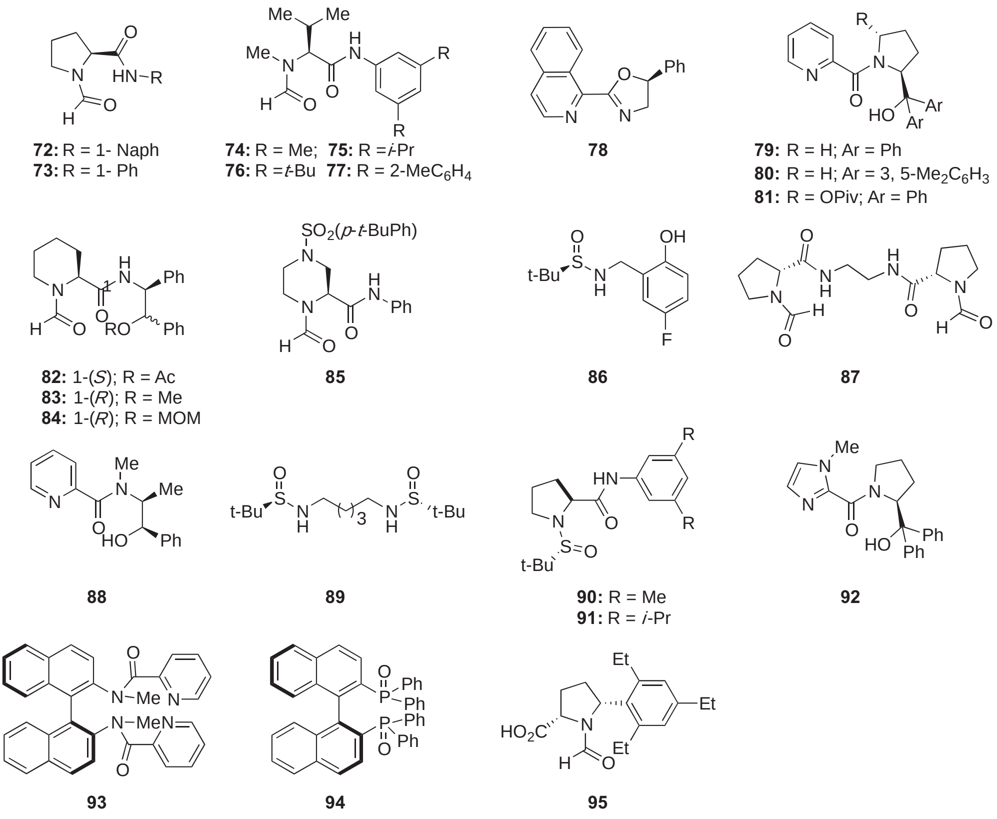
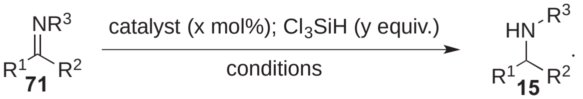


Figure 32.3 Lewis base catalysts.

discovered that Lewis base **78** is efficient for the reduction of *N*-aryl ketimines [48]. The enantioselectivities were high (around 87%) though yields are moderate at about 65%. Soon after this, Matsumura *et al*. found that *N*-picolinoylpyrrolidines (**79**) are good activators for the enantioselective reduction of different kinds of imines, including aromatic ketimines and α-iminoesters, and even work for unprotected enamines, although only moderate yields and ee are obtained (entry 4, Table 32.1) [49]. A survey of catalysts reveals that both the picolinoyl group and carbonyl group are necessary for coordinating the silicon atom. Furthermore, the hydroxyl group is also very important and the authors suggest that it might direct to the nitrogen of the imine via hydrogen bonding.

Based on the previous discovery that trichlorosilyl derivatives could be activated by *N*-formamide-based Lewis base organocatalysts, Sun *et al*. designed a series of novel catalysts (**82** and **83**) derived from L-pipecolinic acid, which features a six-membered ring frame rather than **72** and **73**, which have a five-membered ring derived from L-proline [50]. Surprisingly, both **82** and **83** proved to be superior catalysts for the hydrosilation of *N*-aryl ketimines. Both enantioselectivities and

Table 32.1 Reduction of ketimines by trichlorosilane.



Entry	Catalyst (loading, mol%)	Reaction conditions	R^1, R^2, and R^3	Yield (%) (% ee)	References
1	**72, 73** (10)	Cl_3SiH (1.5 equiv.); DCM, rt, 24 h	R^1 = aryl, R^2 = Me, R^3 = Ph, Bn	52–>99 (49–66)	[46]
2	**74** (10)	Cl_3SiH (1.5 equiv.); $CHCl_3$ or toluene, rt, 16 h	R^1 = aryl, Cy; R^2 = Me; R^2 = Ph, PMP	79–95 (85–92)	[47]
3	**78** (20)	Cl_3SiH (2.0 equiv.); $CHCl_3$, −20 °C, 24 h	R^1 = aryl, R^2 = Me, R^3 = Ph, PMP;	51–65 (85–87)	[48]
4	**79** (10)	Cl_3SiH (1.5 equiv.); DCM, 0 °C to rt, 4 h	R^1 = aryl; R^2 = Me, CO_2Me; R^3 = Ph, Bn;	24–90 (41–80)	[49]
5	**82** (10)	Cl_3SiH (2.0 equiv.); DCM, 0 °C, 16 h	R^1 = aryl, alkyl; R^2 = Me; R^3 = Ph, PMP	75–98 (87–96)	[50a]
6	**85** (10)	Cl_3SiH (2.0 equiv.); $CHCl_3$, −20 °C, 48 h	R^1 = aryl, Cy; R^2 = alkyl; R^3 = Ph	63–99 (82–97)	[51]
7	**86** (20)	Cl_3SiH (2.0 equiv.); DCM, −20 °C	R^1 = aryl, alkyl; R^2 = alkyl; R^3 = Ph, PMP	73–98 (74–93)	[52]
8	**87** (10)	Cl_3SiH (2.0 equiv.); DCM, 0 °C, 16 h	R^1 = aryl, Cy; R^2 = alkyl; R^3 = aryl	74–95 (61–86)	[53]
9	**88** (20)	Cl_3SiH (2.0 equiv.); $CHCl_3$, −10 °C, 24 h	R^1 = aryl, Cy; R^2 = alkyl; R^3 = aryl	70–93 (43–95)	[54]
10	**83** (10)	Cl_3SiH (2.0 equiv.); toluene, −20 °C, 24 h	R^1 = aryl, Cy *i*-Pr; R^2 = Me; R^3 = Ph, PMP;	85–98 (83–93)	[50b]
11	**89** (10)	Cl_3SiH (2.0 equiv.); 2,6-lutidine (30 mol%); toluene, −20 °C, 24 h	R^1 = aryl, Cy *i*-Pr; R^2 = alkyl; R^3 = Ph, PMP	70–95 (72–96)	[55]
12	**90** (10)	Cl_3SiH (2.0 equiv.); toluene or CCl_4, 0 °C, 24 h	R^1 = aryl; R^2 = Me, Et; R^3 = Bn, allyl, alkyl	54–98 (66–99.6)	[56]
13	**92** (1)	Cl_3SiH (2.0 equiv.); DCM, 0 °C, 4 h	R^1 = aryl, Cy; R^2 = Me, Et; R^3 = Ph, PMP	41–96 (19–87)	[57]
14	**93** (10)	Cl_3SiH (2.0 equiv.); DCM, 0 °C, 12 h	R^1 = aryl; R^2 = Me; R^3 = aryl, alkyl	45–99 (71–87)	[58]

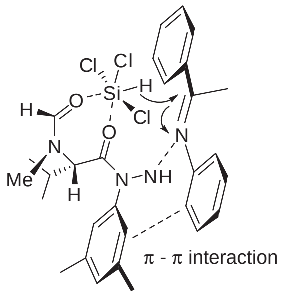


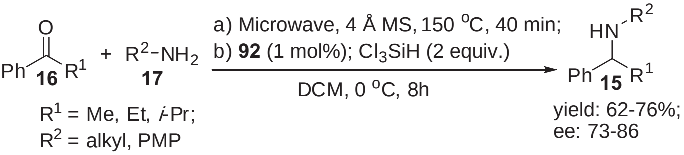
Figure 32.4 Transition state of **74** catalyzed hydrosilation of imine.

yields are high to excellent (entries 5 and 10, Table 32.1). Several months later, the same group reported another *N*-formamide-based chiral catalyst for the same reduction. *N*-Formamide **85**, which could be simply prepared from commercially available L-piperazine-2-carboxylic acid, has been disclosed to be highly efficient for the reduction of *N*-phenyl-ketimines. Enantioselectivities range from 82–97% (entry 6, Table 32.1) [51]. Inspired by allylations with allyltrichlorosilane activated by *S*-chiral sulfoxides [59], Sun *et al.* theorized that chiral sulfinamides might work for the asymmetric hydrosilation of imines. After screening a series of *S*-chiral sulfinamides, they successfully discovered that **85** works well for the enantioselective reduction of *N*-aryl ketimines and offers up to 93% ee [52]. Notably, unlike some previous work, where R^2 is limited to a methyl group, in this work it could be other alkyl groups such as ethyl and *n*-butyl (entry 7, Table 32.1). Based on a clear positive nonlinear effect of catalysis of **86**, the authors realized that the phenolic hydroxyl group of the catalyst probably does not function as a chelating group. Instead, they speculated that the real catalyst might be two **86** molecules bound together through hydrogen bonding of the hydroxyl group; therefore, they decided to put two sulfonamide units into one molecule with a chemical bond instead of a hydrogen bond. They prepared a series of new *S*-chiral bis-sulfinamde catalysts and found the simple catalyst **89** offers the best results in terms of yield and ee. With the aid of 2,6-lutidine as an additive, the enantioselectivity could be improved to 96% (entry 11, Table 32.1) [55]. Sun *et al.* also designed C_2-symmetric chiral tetraamide Lewis base catalysts derived from L-proline, L-valine, and L-pipecolinic acid. Among those catalysts, **87** gave the best results with of 61–86% ee (entry 8, Table 32.1) [53].

Combining key functional groups of Lewis base catalysts **79** and **83**, Zhang *et al.* prepared chiral *N*-picolinoyl-aminoalcohol **88.** This novel catalyst provides moderate to excellent enantioselectivities for the reduction of ketimines, including *N*-benzyl ketimines, in which the benzyl group is easily deprotected (entry 9, Table 32.1) [54].

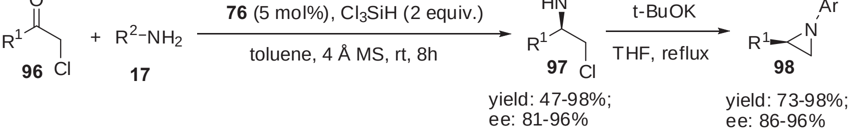
While most successful asymmetric organocatalytic imine reduction methodologies are limited to *N*-aryl imines, Sun *et al.* reported in 2008 that a new chiral sulfinamide catalyst **90** derived from L-proline is highly efficient for the reduction of aromatic *N*-alkyl ketimines. The highest ee is up to 99.6% and the (*E*/*Z*) ratio of the *N*-alkyl ketimines does not show any negative influence on the enantioselectivity (entry 12, Table 32.1) [56]. Binaphthyl is the one of the most successful frameworks utilized in chiral ligands or catalysts. To develop the organocatalytic reduction of *N*-alkyl ketimines, Benaglia *et al.* prepared chiral C_1-symmetric binaphthyl-diamine catalyst **93**, which was found to reduce both *N*-aryl ketimines and *N*-alkyl ketimines with moderate to high enantioselectivities (entry 14, Table 32.1) [58].

In 2009, the imidazole-derived Lewis base catalyst **92**, which was prepared by Jones *et al.*, was employed for the reduction of ketimines with trichlorosilane as the reducing agent. Interestingly, low catalyst loading (as low as 1% mol) works well for this reduction (entry 13, Table 32.1) [57]. During their studies, the authors found that **92** is able to selectively reduce the imine while it is inactive for ketones. Therefore, in 2011, the same group developed an asymmetric reductive amination of ketones **16** catalyzed by **92** with trichlorosilane as the hydride donor (Scheme 32.19). However, the yields for the three-component reaction are moderate. In addition, for the reduction of *N*-alkyl ketimines, a two-step, one-pot procedure plus microwave irradiation is needed to secure a useful synthetic yield [60].



Scheme 32.19

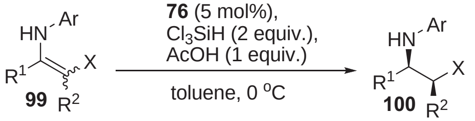
The reductive amination of ketones with useful functional groups would be important in organic synthesis. In 2007, Kocovsky *et al.* proposed that the asymmetric reductive amination product of α-chloroketone **96** could be a precursor for preparing chiral aziridines **98** (Scheme 32.20). After optimizing the reaction conditions they found that sigamide **76** can catalyze the reductive amination reaction to afford corresponding chiral α-chloroamines **97** with up to 96% ee and 98% yield. A further cyclization under basic conditions yields chiral 1,2-diarylaziridines **98** in excellent yield without losing enantioselectivity [61].



Scheme 32.20

32.3.2
Reduction of Enamines

Enamines and imines are tautomers. Only when an enamine tautomerizes to an imine form can it be reduced by a hydride transfer reaction. Fortunately, enamines can be tautomerized to their imine form in the presence of certain Brønsted acids or Lewis acids. Since trichlorosilane is highly sensitive to moisture and, usually, commercial trichlorosilane contains trace amounts of HCl, Kocovsky *et al*. envisioned that an organocatalytic reduction of enamine **99** with trichlorosilane would be possible [62]. Indeed, the reduction catalyzed by sigamide **76** proceeds smoothly to give the desired chiral β-amino ester **100** in 78% yield and 92% ee; however, the reproducibility of the reduction is poor since the concentration of HCl in trichlorosilane is not consistent. The problem is solved by using one equivalent of acetic acid as an additive to tautomerize the enamine to imine, which results in only a slight decrease in enantioselectivity (Scheme 32.21). In addition, moderate to high enantioselectivities (59–90% ee) were obtained for those enamines where R^2 = H. Good enantioselectivities and up to excellent diastereoselectivities were also achieved through a catalytic dynamic kinetic resolution for substrates with R^2 = aryl and alkyl.

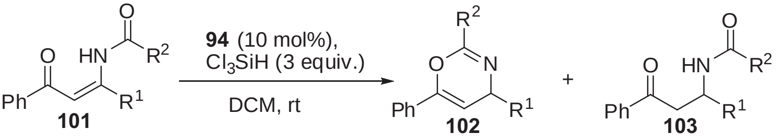


X = CO_2Et, CN;
R^1 = aryl, *i*-Pr; R^2 = H, aryl, alkyl

yield: 26-98%; ee: 59-90%
syn/anti: 27/73 to > 99/1

Scheme 32.21

Sugiura *et al*. tried conjugate reduction of β-amino enone **101** with trichlorosilane catalyzed by **94.** As a result, 4*H*-1,3-oxazine **102** is obtained as the major product, whereas the yield of the desired β-amino carbonyl compound **103** is very low (Scheme 32.22). Furthermore, the ee values of both products are totally different. These results imply that the pathways for producing the two products are different. Based on their observations and previous studies on the conjugate addition of enones with trichlorosilane, the authors proposed that while keto amide



R^1 = Me, Ph, *i*-Pr;
R^2 = aryl, Me

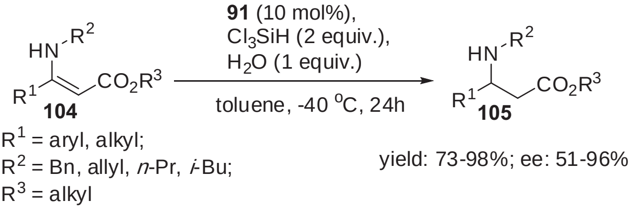
yield: 38-75%
ee: 26-81%

yield: 13-27%
ee: 4-51%

Scheme 32.22

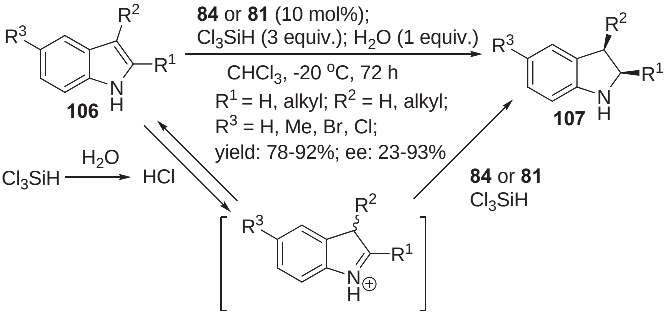
103 is possibly produced by a 1,2-addition of the *N*-acyl imine generated from the enamide **101** via tautomerization, 4*H*-1,3-oxazine **102** is formed from a 1,4-conjugate addition followed by cyclization via an elimination of $HOSiCl_3$ [63].

Very recently, through a similar strategy to that of Kocovsky, Sun *et al.* developed a highly efficient methodology to reduce β-enamino ester **104** for the preparation of chiral β-amino ester **105** (Scheme 32.23). They found that the addition of one equivalent of water to hydrolyze trichlorosilane to generate one equivalent HCl, could greatly increase not only the yield but also the enantioselectivity up to 96%, even though water is usually considered harmful for the reduction with trichlorosilane. Notably, compared with Kocovsky's work where R^2 is limited to an aryl group, this reduction is compatible with alkyl groups such as benzyl, which could be readily deprotected to give free chiral β-enamino ester in excellent enantioselectivity. In addition, R^1 also could be alkyl groups, but only moderate enantioselectivities are obtained [64].



Scheme 32.23

Enantioenriched indolines are very important compounds, which exist extensively in natural alkaloids or unnatural bioactive compounds. The development of facile methods toward chiral indolines continues to be a challenge for organic chemists. Unprotected indole **106** could be considered as a special enamine in an aromatic system. Inspired by the possible shift between enamine and imine of indole in the presence of strong acid, Sun and Chen *et al.* envisioned that a direct reduction of indole **106** to indoline **107** by a combined catalysis of Lewis base and Brønsted acid would be highly possible (Scheme 32.24). Indeed, using the strategy



Scheme 32.24

they previously developed [64], they investigated the reaction conditions and found that Lewis base **84** is the most suitable catalyst. The reduction is general for various indole derivatives, although **81** is found to be a better catalyst for the reduction of some indoles with bulky 2-alkyl groups [65].

32.3.3
Reduction of C=N Bonds Catalyzed by Recoverable Lewis Base Catalysts

One of the most impressive features of organocatalysts is that they are usually recoverable and reusable. In addition, they are relatively easy to support on some recoverable materials such as polymers via stable covalent bonds. To simplify the product isolation procedure, in 2007, after they discovered L-valine derived **74** (Figure 32.4) as an efficient catalyst for the asymmetric hydrosilation of ketimines, Kocovsky *et al.* synthesized **108** with a fluorous ponytail (Figure 32.5). This catalyst exhibits almost equal efficiency with its analog **74** for the reduction of *N*-aryl ketimines, but it could be easily recovered by filtering through a fluorous silica pad [66]. While **108** is a homogeneous catalyst for the reduction, the same group developed a heterogeneous reduction with polymer supported catalyst **109** in 2008 [67]. The reduction catalyzed by this solid-supported catalyst offers a simple recovery operation; however, enantioselectivities (≤82% ee) and yields decreased by about 10–15% points compared with those of homogeneous catalytic systems. To overcome the shortcomings of **109**, the authors turned their attention to soluble polymer-supported catalysts. Copolymer **111** was prepared and employed for the reduction of *N*-PMP ketimines [68]. It was found that the **111** with 0.19 mmol% per g of active moiety is optimal for this reduction and affords up to 88% ee with only 1 mol% catalyst loading. The reaction is homogeneous with toluene as the solvent. After completion, **111** precipitates in a polar solvent, such as methanol, and is recovered for at least five runs without losing activity. Recently, the same

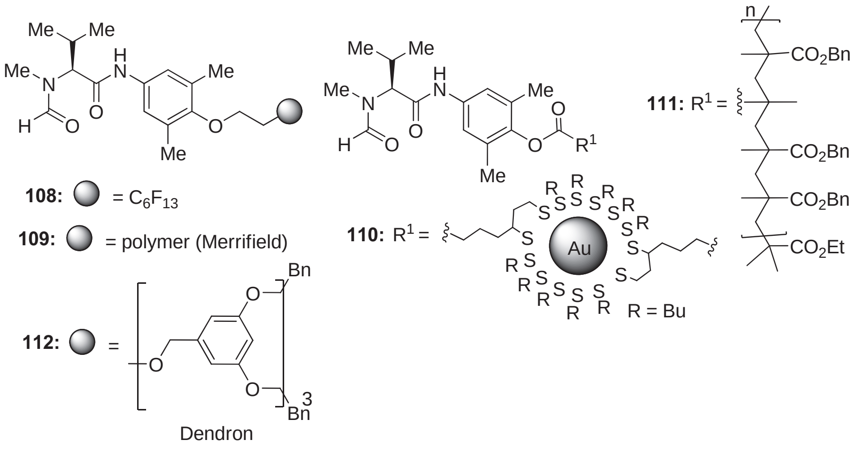


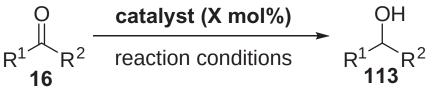
Figure 32.5 Examples of recoverable Lewis base catalysts.

group further improved the results with another recoverable homogeneous catalyst **112**, which was supported on a dendron polymer [69]. This third-generation dendrimer exhibited almost the same activity with sigamide **76**, with ee up to 94%. The recovery of dendrimer **112** is similar to that of soluble polymer-supported catalyst **111**. Another interesting gold nanoparticle supported catalyst (**110**) has also been reported by Kocovsky *et al.* [70]. This inorganic material supported catalyst is soluble in non-polar solvents, such as toluene, and could be recovered by precipitating in methanol. However, considerable deterioration of enantioselectivity occurred after recovering three times. This is possibly due to the immobilized organocatalyst becoming detached from the gold nanoparticles.

32.3.4
Asymmetric Reduction of C=O Bonds

Since it was found that silane could be activated by Lewis bases such as DMF [71], research towards nucleophilic addition with silane was rejuvenated. In 1999, Matsumura *et al.* reported the first catalytic asymmetric reduction of ketones with trichlorosilane as the reducing agent [45]. In this report, the L-proline derived *N*-formamide **72** or **73** is found to be a potential catalyst for activating trichlorosilane to function as an active reducing agent. However, only low to moderate enantioselectivities are obtained (8–51%) (entry 1, Table 32.2). Several years later, after achieving success for the imine reduction with Lewis base catalysis, Matsumura *et al.* improved the ketone reduction chemistry with a new catalyst **95** (entry 2, Table 32.2) [72]. After screening various Lewis base catalysts, **95** proved

Table 32.2 Asymmetric reduction of ketones with trichlorosilane.



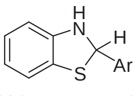
Entry	Lewis base catalyst (loading, mol%)	Reaction conditions	R^1, R^2	Yield (%) (% ee)	References
1	**72** or **73** (10)	Cl_3SiCH (1.5 equiv.); DCM, 0 °C to rt, 24 h	R^1 = aryl, phenylethyl; R^2 = Me, Et, Pr^i, Bn	21–87 (8–51)	[45]
2	**95** (10)	Cl_3SiCH (3.0 equiv.); $CHCl_3$, rt, 24 h	R^1 = aryl, ferrocenyl; R^2 = Me, Pr, $CH_2CH_2CO_2Et$	61–98 (93–99.7)	[72]
3	**83** (10)	Cl_3SiCH (3.0 equiv.); toluene, −20 °C, 16 h	R^1 = aryl, alkyl; R^2 = Me	81–99 (53–93)	[50b]

to be the best and provides excellent enantioselectivities for the reduction of various aromatic ketones (up to 99.7% ee). In 2007, Sun *et al.* reported another ketone reduction with Lewis base catalyst **83.** This catalytic system is not only efficient for aromatic ketones, but also works for aliphatic ketones, nevertheless with moderate enantioselectivities (entry 3, Table 32.2) [50b].

32.4
Other Hydrogen Sources

32.4.1
Benzothiazolines

Although Hantzsch esters proved to be an efficient and mild reductant for asymmetric organocatalysis, disadvantages such as high cost and low atom economy limit its application. Therefore, novel biomimetic hydrogen sources are still highly desired. In 2009, Akiyama *et al.* noticed that benzothiazolines (benzothiazoles, Figure 32.6), which are efficient antioxidants, might function as suitable agents for reducing imines. Indeed, after a detailed survey of various benzothiazoline derivatives and chiral phosphoric acids, they discovered that the combination of catalyst **3** and reductant benzothiazoline **114** (Figure 32.6) gives the best enantioselectivity (up to 98%) for the reduction of *N*-PMP ketimines **14** (Scheme 32.25) [73]. Notably, benzothiazoline could be generated *in situ* for this reduction chemistry while still providing excellent ee and only a slightly decrease in yield. A year later, the same authors successfully extended this catalytic system to the asymmetric reduction of α-imino esters **24**, obtaining excellent yields and ee with benzothiazoline **115** as the hydrogen donor (Scheme 32.26) [74]. Furthermore, to solve the isolation problem brought about by the benzothiazole by-product, the authors prepared **116,** with a polar hydroxyl group on the phenyl ring, and found that the benzothiazole by-product of **116** precipitates during the reaction and could be easily filtered off. The reduction ability of benzothiazole is further exhibited in the transfer hydrogenation of ketimines **119** derived from aromatic trifluoromethyl ketones (Scheme 32.27) [75]. Owing to the considerable attention that had been paid to fluorinated compounds, Akiyama *et al.* were interested in the synthesis of chiral trifluoromethylated amines **120.** Based on previous success with the

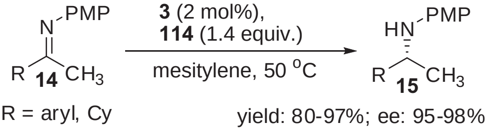


114: Ar = 2-naphthyl
115: Ar = phenyl
116: Ar = p-OHC$_6$H$_4$
117: Ar = p-C$_6$H$_5$C$_6$H$_4$
118: Ar = p-NO$_2$C$_6$H$_4$

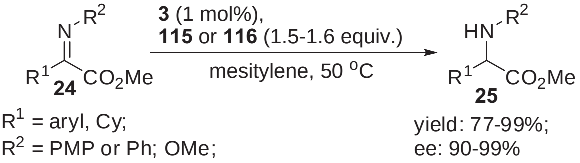
Figure 32.6 Some benzothiazolines used as a reductant.

reduction chemistry using benzothiazoles, the authors realized the asymmetric reduction of trifluoromethylated imines **119.** The transfer hydrogenation accommodates various aromatic chiral trifluoromethylated amines **120** with excellent ee (96–98% ee); meanwhile, the same reduction with Hantzsch ester **1a** gives 4% yield of amine product with 45% ee. The potential synthetic utility of this chemistry has been demonstrated by the transformation of one of the amine products into the trifluoromethylated analog of NPS R-568 (**121**) with 97% ee.

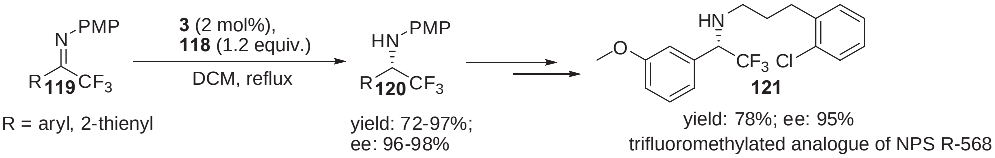
Tetrahydroisoquinolines are fundamental moieties found in natural and biologically active compounds. Enders *et al.* considered that chiral 1,3-disubstituted tetrahydroisoquinolines **123** could be synthesized via an organocatalytic reductive amination and aza-Michael addition sequence (Scheme 32.28) [76]. During optimization of the reaction conditions, they found that hydrogen source benzothiazole **117** provides a much higher yield than that of Hantzsch ester **1a** but slightly decreases the enantioselectivity. After changing the EWG group to bulky esters or amides, they obtained excellent yields and ee for the reaction sequence (93–98% ee).



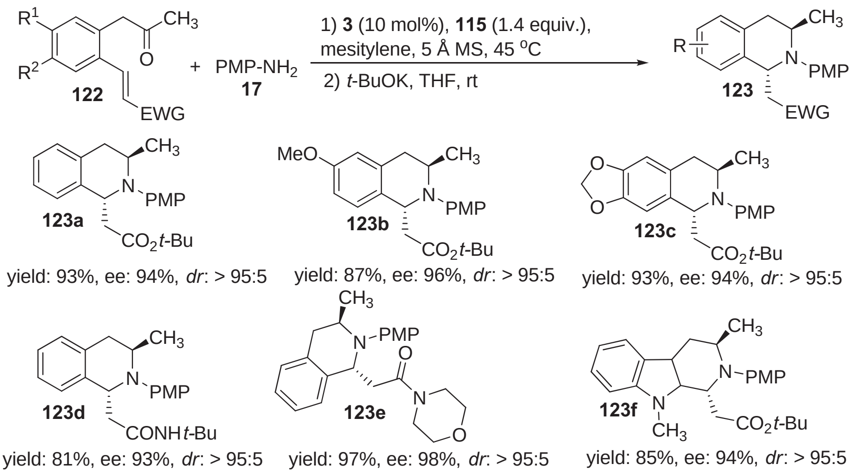
Scheme 32.25



Scheme 32.26



Scheme 32.27

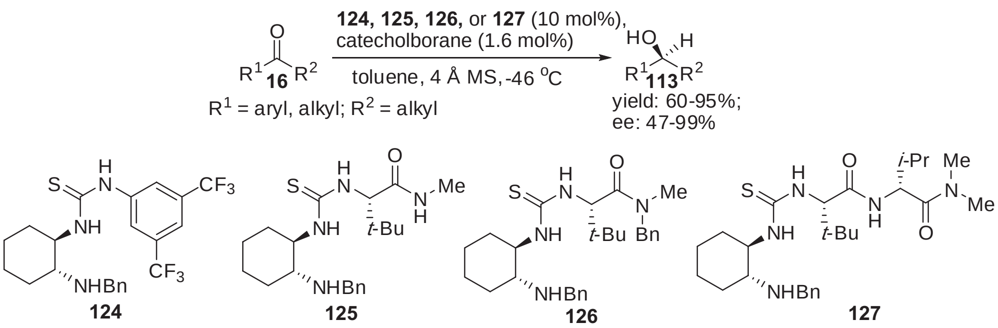

122
17
1) 3 (10 mol%), 115 (1.4 equiv.), mesitylene, 5 Å MS, 45 °C
2) t-BuOK, THF, rt
123
123a
yield: 93%, ee: 94%, dr: > 95:5
123b
yield: 87%, ee: 96%, dr: > 95:5
123c
yield: 93%, ee: 94%, dr: > 95:5
123d
yield: 81%, ee: 93%, dr: > 95:5
123e
yield: 97%, ee: 98%, dr: > 95:5
123f
yield: 85%, ee: 94%, dr: > 95:5

Scheme 32.28

32.4.2
Boranes

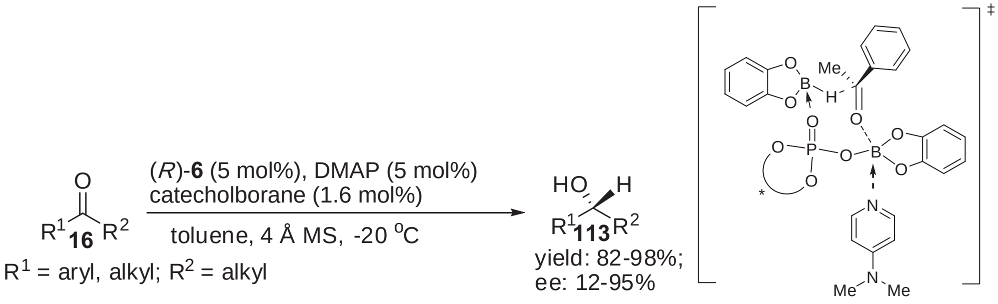
Borane is one of the most common agents for reducing C=O and C=N bonds and its applications for the enantioselective reduction of ketones and imines have been extensively studied in past decades [77]. Among such agents, the Corey–Bakshi–Shibata (CBS) catalyst, a chiral oxazaborolidine complex, which was discovered by Itsuno in 1981 [78] and further developed by Corey in 1987 [79], was widely considered as the most successful catalytic system. Several excellent reviews are already available [77a, 80]. In this chapter, we only give limited coverage of the organocatalytic asymmetric reduction of ketones by catalytic systems other than chiral oxazaborolidines.

Despite numerous highly enantioselective organic transformations developed with chiral thioureas in the last decade, there are few examples of successful asymmetric reduction. Based on their research on the asymmetric oxy-Michael additions of boronic acids with α,β-unsaturated ketones [81], Falck *et al.* realized that a chiral thiourea-amine (Scheme 32.29) organocatalyst might function for the borane reduction of ketones since the amine moiety of the bifunctional thiourea could coordinate with borane and the thiourea moiety might activate the carbonyl of the ketone **16** (Scheme 32.29) [82]. After a survey of reaction conditions, the authors discovered that thiourea **124** exhibits excellent stereoselectivity for the reduction of aromatic ketones (95–99% ee). Notably, the *N*-benzyl protective group in the thiourea catalysts is found to be indispensable for inducing high enantioselectivity. This might suggest that a π–π stacking effect exists between the *N*-benzyl group and catecholborane.


124, 125, 126, or 127 (10 mol%),
catecholborane (1.6 mol%)
toluene, 4 Å MS, -46 °C
16
R1 = aryl, alkyl; R2 = alkyl
113
yield: 60-95%;
ee: 47-99%
124
125
126
127

Scheme 32.29

Another breakthrough came from Antilla *et al.*, who employed a chiral phosphoric acid as an efficient catalyst for the reduction of prochiral ketones [83]. As an extension of their success in the enantioselective allylation of aldehydes with allyl borate [84], they hypothesized that a chiral phosphoric could activate and direct the borane reduction of ketones. Initial studies showed that the asymmetric reduction truly works and, after screening various chiral phosphoric acids, found that **6** stands out as the most suitable catalyst. The enantioselectivity is further improved by using 4-(dimethylamino)pyridine (DMAP) as an additive (ee up to 95%) (Scheme 32.30). To gain mechanistic insight into this reduction, the authors performed several parallel ^{11}B NMR experiments; the results suggest that the complex formed between **6**, catechol borate, and DMAP might be the real catalyst for the asymmetric reduction.

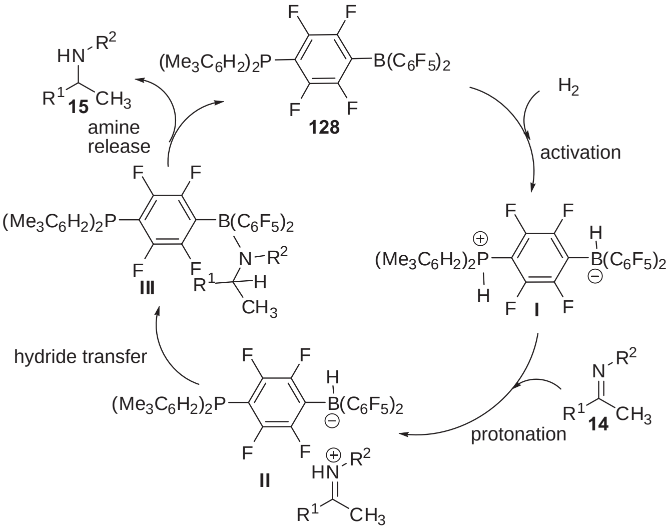

(R)-6 (5 mol%), DMAP (5 mol%)
catecholborane (1.6 mol%)
toluene, 4 Å MS, -20 °C
16
R1 = aryl, alkyl; R2 = alkyl
113
yield: 82-98%;
ee: 12-95%
‡

Scheme 32.30

32.4.3
Hydrogen as the Source?

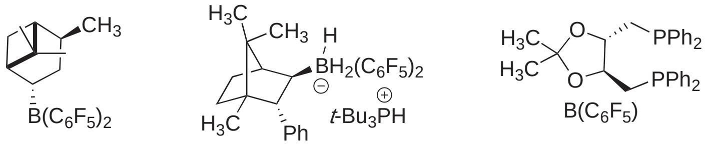
32.4.3.1 Chiral Frustrated Lewis Pairs as Catalysts

There is no doubt that hydrogen gas is the best hydrogen source for hydrogenation in terms of both atom economy and cost economy. However, usually, certain complexes of transition or rare metal such as palladium, iridium, platinum, rhodium, or ruthenium are necessary to activate hydrogen due to its considerable inertness for chemical reactions [1d, 85]. Organocatalysis has been one of the primary research areas in organic chemistry since the beginning of the new century [86]. Are there any metal-free catalysts for enantioselective hydrogenation by H_2? The phenomenon of forming a stable pair between a bulky Lewis acid and base rather than neutralizing each other was observed by organic chemists 70 years ago [87]; however, only much more recently, Stephan *et al.* reported that this kind of steric hindered Lewis pair is able to activate H_2 even at room temperature (Scheme 32.31) [88]. They termed such a molecule as a sterically "frustrated Lewis pair (FLP)." Since there are elegant reviews [89] available we will not cover this exciting subject in detail here. Instead, we introduce the progress of FLPs as an organocatalyst in the asymmetric reduction of imines.



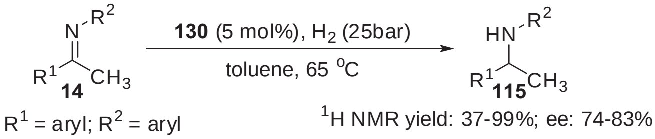
Scheme 32.31

The power of FLPs for catalytic hydrogenation of imines has been demonstrated by several research groups. Therefore, the possibility of developing its asymmetric version has been examined by organic chemists. In 2008, Klankermayer *et al.* described a metal-free catalytic hydrogenation of imines with tris(perfluorophenyl) borane. In this work, they employed a chiral borane catalyst (**129**, Figure 32.7) and obtained a low enantioselectivity (13% ee), in what was a first attempt [90]. Two years later, the same group made great progress with the chiral FLP catalyzed imine reduction. They reported that in the presence of 5 mol% **130** various aromatic imines (**14**) are reduced by hydrogen gas to afford the corresponding amines with moderate to high ee (74–83%) (Scheme 32.32). Even though the reduction of bulky 2,6-diisopropyl-*N*-(1-phenylethylidene)aniline does not work under the reported reaction conditions, this study still represents a significant advance for



129 **130** **131**

Figure 32.7 Examples of sterically frustrated Lewis pair (FLP) molecules.

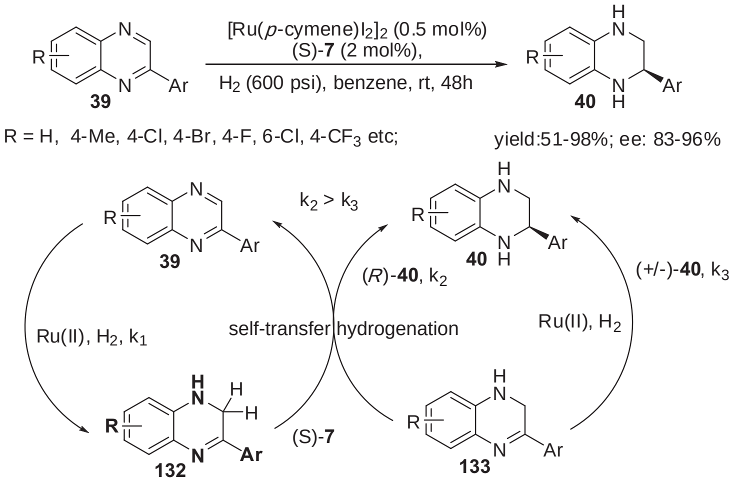


Scheme 32.32

chiral FLP catalyzed asymmetric hydrogenation [91]. Stephan *et al.* attempted to employ chiral phosphines for the hydrogenation of imines but obtained only 25% ee with (*S,S*)-diop/$B(C_6F_5)$ (**131**) as catalyst [89a]. They reasoned that the role of the phosphonium cation (I, Scheme 32.31) is to transfer a proton to the imine whereas the hydrogen bonding between the phosphine and NH is not strong enough to induce a decent enantioselectivity (II, Scheme 32.31).

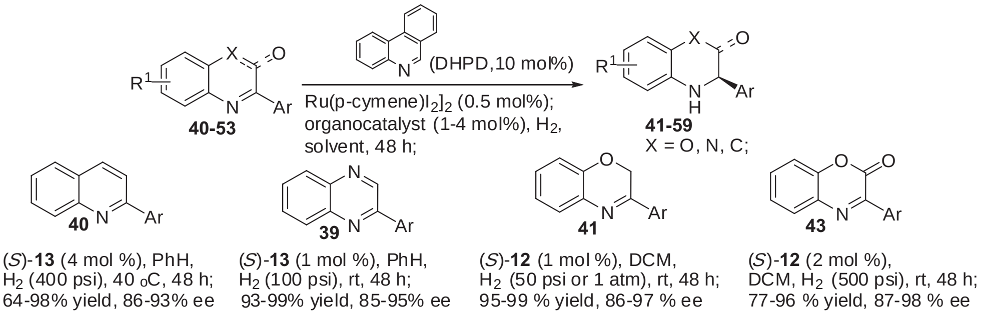
32.4.3.2 H_2 as a Terminal Hydrogen Source: Combined Hydrogenation by Organocatalysis and Metal Catalysis

The Hantzsch ester has been demonstrated as one of the most successful biomimetic hydride donors in synthetic chemistry and has been employed in the highly enantioselective organocatalytic hydrogenation of unsaturated bonds, especially for C=N bonds. However, as previously mentioned, it also suffers from disadvantages such as very low atom economy. Therefore, developing easily regenerable organic hydride sources would be highly desirable. Recently, Zhou *et al.* developed an elegant combined catalysis for *in situ* regeneration of Hantzsch ester from its pyridine by-product through metal-catalyzed hydrogenation with H_2 as the hydrogen source [37]. During their studies, they unexpectedly discovered there is a disproportionation reaction of dihydroquinoxaline **132.** In the presence of chiral phosphoric acid (*S*)-**7**, the self-transfer hydrogenation of dihydroquinoxaline **132** affords chiral tetrahydroquinoxaline **40** with 93% ee, while dihydroquinoxaline **132** could be *in situ* regenerated by hydrogenation with hydrogen gas catalyzed by a Ru(II) complex (Scheme 32.33). This combined catalysis has proven to be quite general for various quinoxalines **39** with enantioselectivities in the range 83–96%. The authors proposed that in the catalytic cycle the hydrogenation of **39** to **132** catalyzed by Ru(II) complex is the rate-determining-step. However, in the second step, the hydride transfer reaction of **132** catalyzed by **7** is much faster than its hydrogenation catalyzed by ruthenium(II) ($k_2 > k_3$). Thus, it leads to high enantioselectivity rather than racemic results [92].


[Ru(p-cymene)I2]2 (0.5 mol%)
(S)-7 (2 mol%),
H2 (600 psi), benzene, rt, 48h
39
40
R = H, 4-Me, 4-Cl, 4-Br, 4-F, 6-Cl, 4-CF3 etc;
yield:51-98%; ee: 83-96%
k2 > k3
(R)-40, k2
(+/-)-40, k3
Ru(II), H2, k1
self-transfer hydrogenation
Ru(II), H2
(S)-7
132
133

Scheme 32.33

Based on previous success, Zhou *et al.* realized that the dihydropyridine amido group might be the key structure for hydride donors such as Hantzsch ester **1** and dihydroquinoxaline **132** and, if so, 9,10-dihydrophenanthridine (DHPD), due to its high potency of dehydroaromatization, might be able to serve as a hydride donor for the organocatalytic hydrogenation. Indeed, DHPD is able to reduce benzoxazinone **53** to chiral dihydrobenzoxazinone **59** in the presence of (*S*)-**12** with high to excellent enantioselectivities; meanwhile, DHPD itself could be regenerated by hydrogenation of H_2 catalyzed by a Ru(II) complex (Scheme 32.34). Therefore, only catalytic DHPD (10 mol%) is needed for this biomimetic hydrogenation, and hydrogen is the terminal reducing agent. Owing to the good reactivity of DHPD, this catalytic system is also highly efficient for the reduction of benzoxazines **41**, quinoxalines **39**, and quinolines **40** [93].



Scheme 32.34

32.5
Summary and Conclusions

Rapidly growing interest has been paid worldwide to the research area of asymmetric organocatalysis since 2000. In the past few years, dramatic advancements have been made for asymmetric organocatalytic hydrogenation. This includes the development of novel catalytic systems, new activation modes, and new organic transformations. Among them, chiral Brønsted acid mediated enantioselective transfer hydrogenation has emerged as a new, general, and powerful method for reducing imines to chiral amines with Hantzsch ester, a biomimetic analog of NADH, as the hydride source. Recently, an exciting hydrogen activation model with "frustrated Lewis pairs" as metal-free catalysts has appeared and very promising preliminary results of asymmetric hydrogenation imines have been achieved. Even so, compared with the traditional enantioselective hydrogenation model of "metal plus chiral ligand," organocatalytic asymmetric hydrogenation is still in its infancy and limitations, including the diversity of organocatalysts, types of reactions, scope of substrates, and catalytic efficiency, need to be further addressed in the future.

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Part III
Nucleophile Addition to C=C Bonds

33

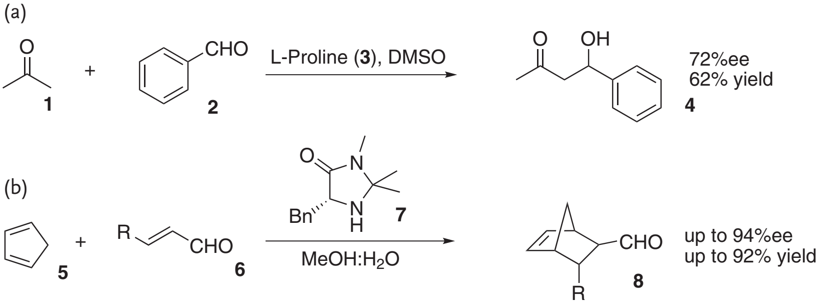
Addition to α,β-Unsaturated Aldehydes and Ketones

Ramon Rios[1] *and Xavier Companyó*

33.1
Introduction

In the last decade, organocatalysis has been developed as a powerful tool for the synthesis of complex molecules [1]. For example, amine catalysis allows the development of new and highly enantioselective methodologies for the asymmetric synthesis of new C-atom bonds.

The beginning of this new era can be traced to the pioneering works of List, Barbas, and Lerner in enamine chemistry [2] and MacMillan and coworkers in iminium chemistry (Scheme 33.1) [3].



Scheme 33.1 Earlier examples from (a) List and (b) MacMillan.

These two methodologies are complementary. While List, Lerner, and Barbas' methodology allows the electrophilic attack of the "*in situ*" enamine formed, MacMillan's methodology consists of the activation of α,β-unsaturated aldehydes to undergoes nucleophilic addition.

In this chapter cover the most important processes for nucleophilic addition to α,β-unsaturated aldehydes and ketones based on organocatalysis.

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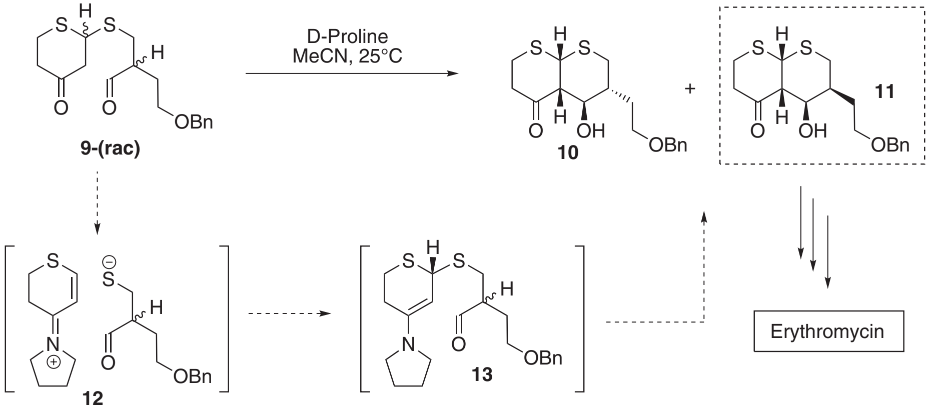
33.1.1
Iminium Activation

33.1.1.1 Historical Overview

The roots of iminium activation can be traced back to the pioneering works of Knoevenagel [4]. The Knoevenagel condensation became the first reaction that might proceed via iminium catalysis. Next, Pollack reported that several proteins and amino acids catalyzed the decarboxylation of acetoacetic acid. The mechanism suggested by Petersen involves an imine intermediate [5].

In 1937, Langenbeck reported the first iminium catalyzed conjugated addition. *N*-Methylglycine and piperidinium acetate were found to be good catalysts for the conjugate addition of water to crotonaldehyde [6].

Probably the most outstanding work in iminium catalysis before its rebirth in 2000 was the synthesis of erythromycin reported by Woodward *et al.* [7]. In this work, Woodward applied proline catalysis in a triple organocascade reaction consisting of a deracemization (via a retro-Michael, Michael addition) and an intramolecular aldol reaction that determines the stereochemical output of the reaction (Scheme 33.2).



Scheme 33.2 Triple organocascade reaction reported by Woodward.

Yamaguchi and coworkers reported in the early 1990s the use of alkali metal salts of proline (e.g., rubidium prolinate) for the conjugate addition of malonates to enals with promising results [8]. Soon after, Taguchi and coworker developed a similar reaction using (2-pyrrolidyl)(alkyl)ammonium hydroxide as catalyst [9].

33.2
Nucleophilic Addition to Enals and Ketones

33.2.1
Iminium Activation

Since its rediscovery by MacMillan in 2000, iminium activation catalysis has become a key catalytic concept in organocatalysis. After initial work centered on cycloadditions, Michael additions became the main area of interest and it is now established as a general strategy for the asymmetric conjugate addition of nucleophiles to α,β-unsaturated compounds.

The concept of this strategy was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α,β-unsaturated aldehydes and chiral amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis [i.e., lowest-unoccupied molecular orbital (LUMO)–lowering activation] as shown in Figure 33.1.

The generally accepted mechanism for these reactions begins with the acid-promoted condensation of the carbonyl moiety with the amine to form an unsaturated iminium ion. This reactive intermediate then suffers the addition of the nucleophile at the β-position, leading to a β-functionalized enamine that could render, after protonation, a saturated iminium ion, or could undergo a cascade reaction with a suitable electrophile. Hydrolysis of these saturated iminium ions releases both the product and the catalyst (Figure 33.2).

In the case of enals, the most common catalysts are secondary chiral amines, which can be divided into two large groups: (i) amines substituted with a bulky group and (ii) amines with hydrogen-bond-directing groups. Another possible type of catalyst for this activation mode arises from ACDC (asymmetric counterion direct catalysis) developed by List. In these catalysts either a chiral or non-chiral amine forms a chiral ionic pair with a chiral phosphoric acid. A different possibility is the use of a primary chiral amine and a strong acid. These latter methods have

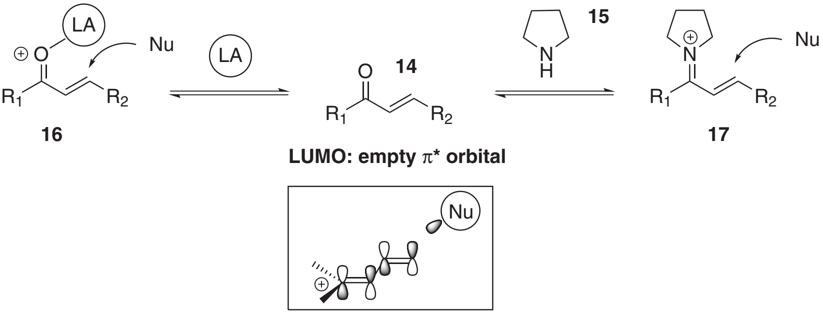


Figure 33.1 Iminium activation.

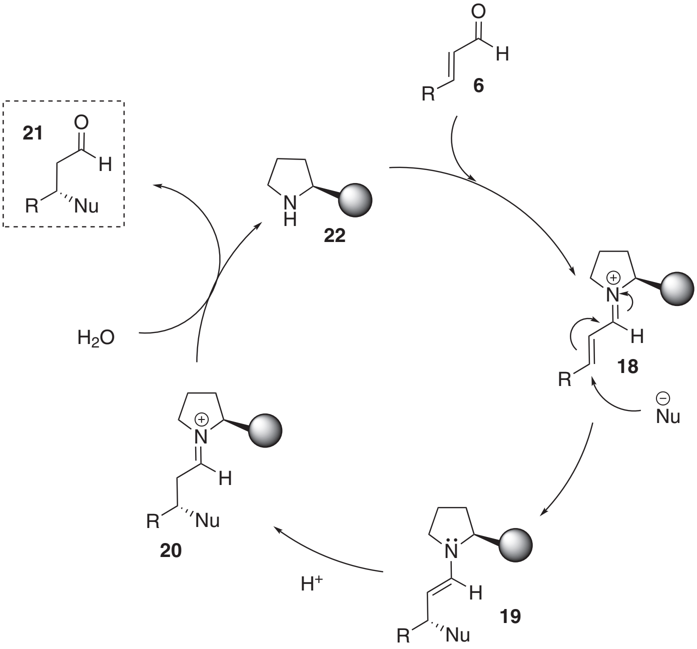


Figure 33.2 Mechanism of iminium activation with secondary amines.

shown excellent efficiency in the nucleophilic addition to enones and α-substituted enals.

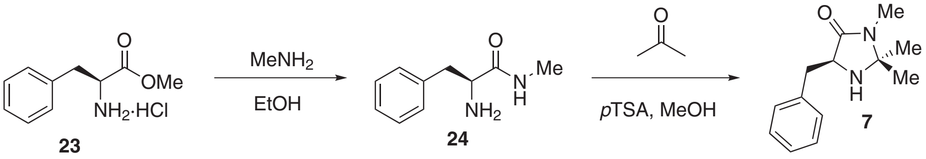
33.2.1.1 Catalyzed by Secondary Amines

33.2.1.1.1 Catalyzed by Secondary Amines Substituted with Bulky Groups

Mechanism After the first report of iminium activation by MacMillan *et al.* in 2000, many studies have been made in this area. Two of the most important families of catalysts are MacMillan's catalysts and the TMS *O*-protected diaryl substituted prolinols developed independently by Jørgensen and Hayashi in 2005.

The commonly accepted stereochemical outcome for such catalysts is depicted in Figure 33.2. This mechanism implies attack of the electrophile by the face opposite the bulky amine substituent, in the energetically favored *s*-trans conformer of the (*E*)-configured unsaturated iminium ion.

Catalysts In the last decade, several catalysts have been developed based on the concept of chiral secondary amines bearing a bulky substituent. MacMillan and coworkers have developed a family of chiral imidazolines derived from α-amino acids (Scheme 33.3).



Scheme 33.3 General synthesis for MacMillan's imidazoline catalyst.

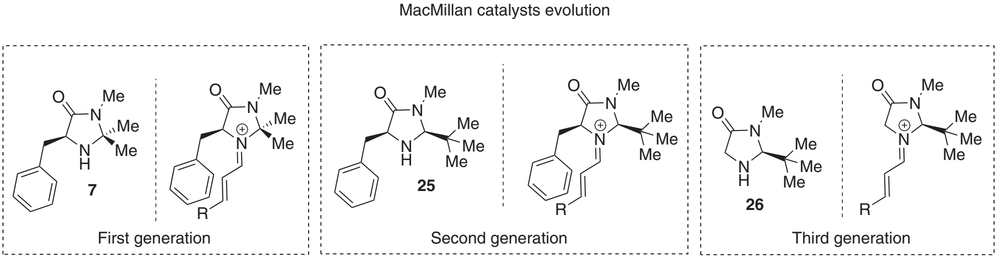


Figure 33.3 Evolution of MacMillan catalysts and the corresponding iminium catalysts.

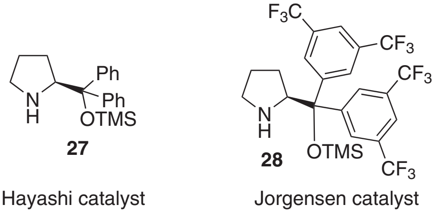


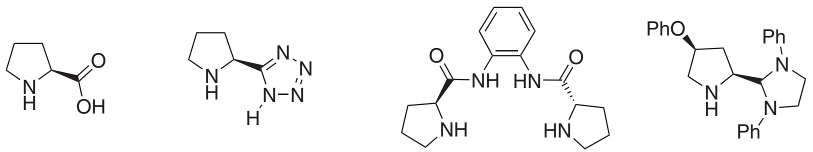
Figure 33.4 Hayashi and Jørgensen catalysts.

Since the first catalyst (**7**) used in the organocatalytic Diels–Alder reaction, several modifications have been made to improve its catalytic properties. In 2002 the commonly called MacMillan second-generation catalyst (**25**) was used in the addition of indoles to enals [10]. A few years later, MacMillan's third-generation catalyst (**26**) was used for the enantioselective transfer hydrogenation of enals (Figure 33.3) [11].

In 2005 Jørgensen [12] and Hayashi [13] developed almost at the same time diarylprolinol derivatives protected as silyl ethers (Figure 33.4) as a suitable catalysts for imine and enamine activation.

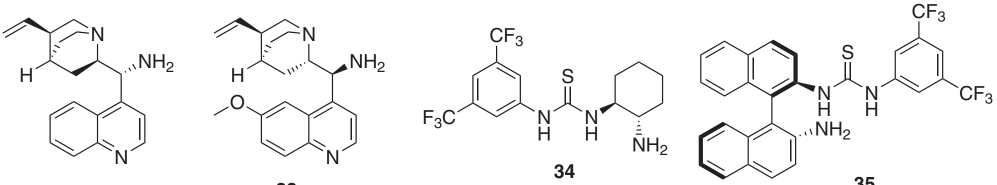
33.2.1.1.2 **Catalyzed by Secondary Amines Substituted with Hydrogen-Bond-Directing Groups**

Mechanism Secondary amines bearing hydrogen-bond directing groups have often been used in the activation of cyclic enones. The commonly accepted



3 **29** **30** **31**

Figure 33.5 Example of secondary amine catalysts bearing a hydrogen donor group.



32 **33** **34** **35**

Figure 33.6 Primary amine catalysts.

mechanism for such catalysts implies that the attack of the electrophile takes place in an intramolecular fashion, via a cyclic transition state, by the same face to the hydrogen bond group substituent, in the energetically favored *s*-trans conformer of the (*E*)-configured unsaturated iminium ion.

Catalysts Most catalysts of this type are proline derivatives, bearing different groups such as thioureas, amides, and so on (Figure 33.5).

33.2.1.2 **Primary Amine Catalysis**

Primary amine catalysts have been used almost exclusively for the activation of enones or α-substituted enals due to the low reactivity of the secondary amine catalysts described below with these substrates. The stereochemical course of the reaction is highly dependent on the nature of the primary amine and in most cases is difficult to rationalize. The most common primary amines used as catalysts are cinchona alkaloid derivatives, chiral diamines, or BINAM derivatives (Figure 33.6).

33.2.1.3 **ACDC Catalysts**

Asymmetric counterion direct catalysis (ACDC) was first reported by List in 2006 [14]. List was intrigued by the observation of a strong counterion effect on the yield and enantioselectivity in iminium catalyzed reactions, hypothesizing that catalytic salts of achiral amines (primary or secondary) and chiral phosphoric acids could induce asymmetry in the process. Later on, this powerful methodology was extended to other chiral acids or even to the combination of chiral amines and chiral acids. Rationalization of the stereochemical course of the reaction is almost impossible due the nature of the ion pair (Figure 33.7).

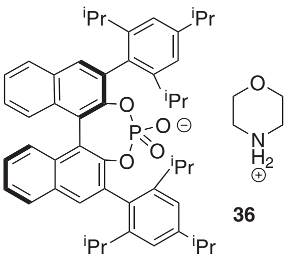


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Figure 33.7 Example of an asymmetric counterion direct catalysis (ACDC) catalyst.

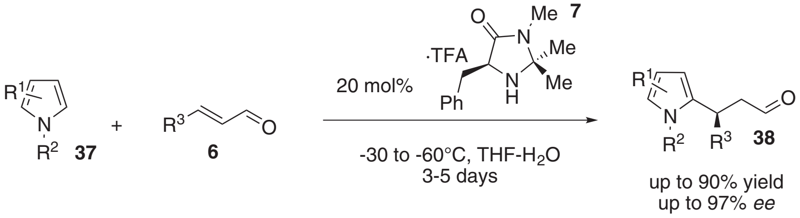
33.2.2
Scope of the Nucleophilic Addition to Enals

Since the first report from MacMillan in 2000 [3], the research community has devoted many efforts to the development of new methodologies based on the iminium activation of enals for the enantioselective construction of C–X bonds. Activation of the β position of the enal allows the attack of different nucleophiles. During the last decade carbon, nitrogen, oxygen, sulfur, or phosphorus nucleophiles have been used to form new stereogenic bonds with high levels of rate and stereoselectivity. In this chapter we describe the most important procedures developed in the field, taking into account the nature of the bond formed and avoiding as much as possible electrocyclic or tandem reactions that would be described in other chapters.

33.2.2.1 C–C Bond Formation

33.2.2.1.1 Conjugate Friedel–Craft Alkylation

The first organocatalytic asymmetric carbon nucleophilic addition to enals was reported by MacMillan in 2001 [15]. MacMillan reported the first Friedel–Craft alkylation between N-substituted pyrroles and enals promoted by catalyst **7.** The reaction renders the final compounds in good yields and enantioselectivities (Scheme 33.4).

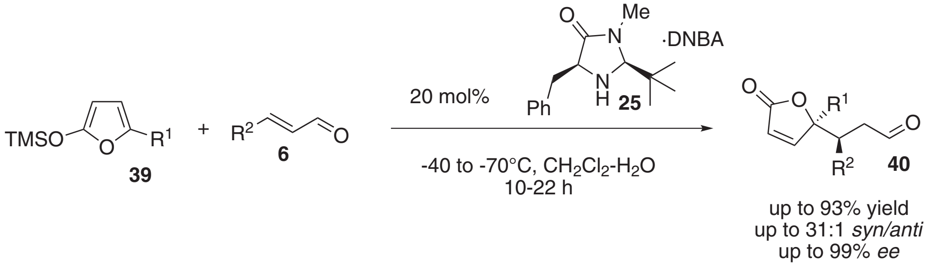


Scheme 33.4 Friedel–Craft reaction of enals.

In 2002 the same research group extended this methodology to electron-rich benzenes with excellent results [16].

33.2.2.1.2 **Mukaiyama–Michael Reaction**

In 2003, MacMillan and coworkers developed the first enantioselective organocatalytic Mukaiyama–Michael reaction that give access to a enantioenriched γ-butenolide architectures [17]. The reaction was efficiently catalyzed by MacMillan second-generation catalyst **25**, and renders the final compounds with excellent yields and enantioselectivities; the scope of the reaction is wide, allowing the use of almost any substituent in the β position of the enal without a substantial change in yield or diastereo- or enantioselectivities (Scheme 33.5). MacMillan and coworkers applied this methodology for the synthesis of spiculisporic acid and 5-epi-spiculisporic acid with excellent results. In 2005, Wei Wang and coworkers expanded the scope of this reaction by using different silyl enol ethers as suitable nucleophiles [18]. In 2009, MacMillan and coworkers reported an improved methodology for a general Mukaiyama–aldol reaction with enals [19].

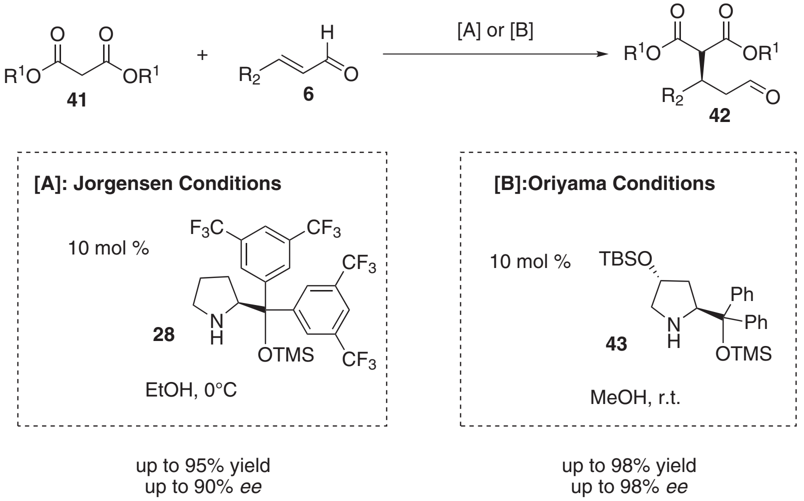


Scheme 33.5 Mukaiyama reaction reported by MacMillan.

33.2.2.1.3 **Michael Reaction of Acidic C–H Bonds**

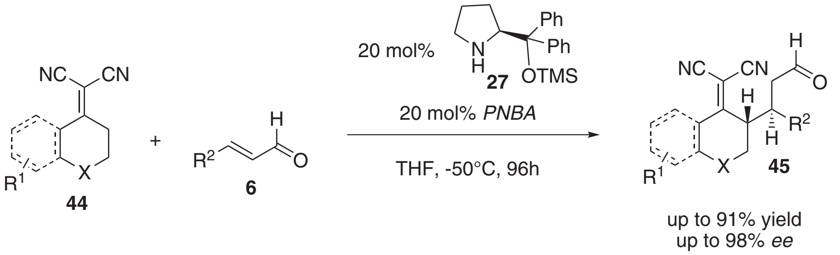
One of the first 1,3-dicarbonylic carbon nucleophiles added in asymmetric fashion to iminium activated enals was malonates. In 2006, Jørgensen *et al.* reported the reaction between malonates and enals catalyzed by catalyst **28** [20]. The final products **42** were obtained in good yields and excellent enantioselectivities. The only limitation of this methodology is that only aromatic enals could be used. To overcome this limitation, Oriyama and coworkers employed catalyst **43** to promote the reaction between crotonaldehyde and malonates in moderate yields and enantioselectivities (Scheme 33.6) [21].

Based on the pioneering report of Jørgensen, his research group and some other groups have developed several analogues with diphenylprolinol derivatives bearing an ionic liquid fragment as catalysts [22], using fluoromalonates [23], cyanoesters [24], or 4-hydroxycoumarins [25] instead of malonates or developing powerful cascade reactions with malonate derivatives [26]. In 2006, Deng and coworkers



Scheme 33.6 Addition of malonates to enals.

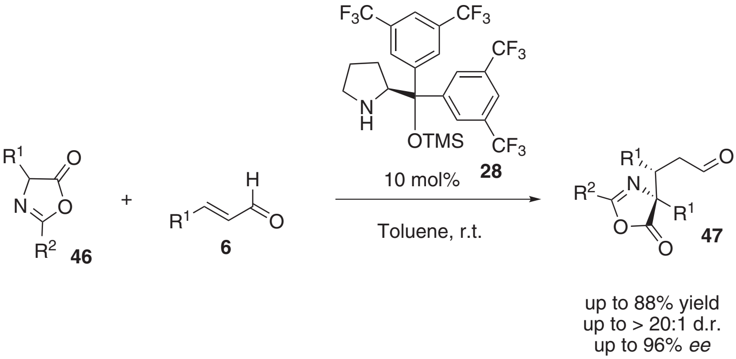
developed the first vinylogous Michael addition of α,α-dicyanoolefins to enals [27]. The reaction was efficiently catalyzed by **27**, achieving the final products, which have two vicinal chiral tertiary and carbon centers, in high regio-, chemo-, diastereo-, and enantioselectivities (Scheme 33.7).



Scheme 33.7 Deng reaction.

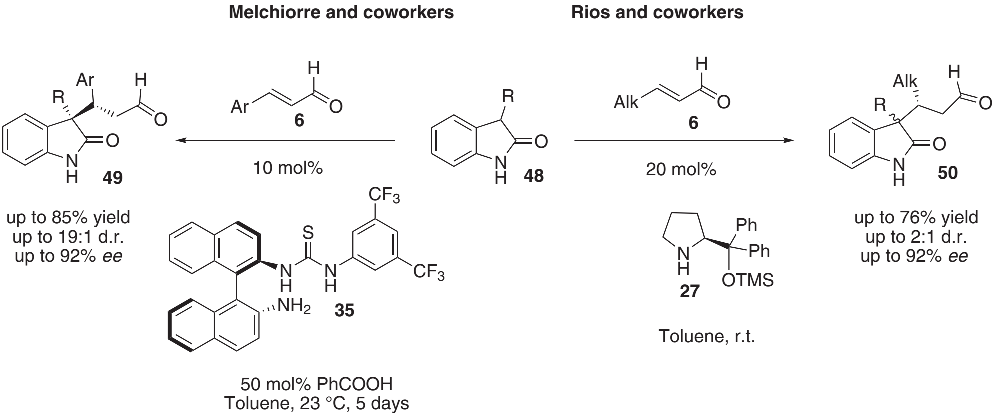
In 2008, Jørgensen and coworkers developed an extremely powerful methodology for the synthesis of α,α-disubstituted amino acids via a Michael addition of oxazolones to enals [28]. The reaction was catalyzed by catalyst **28** and renders the final amino acid precursors in good yields and excellent diastereo- and enantioselectivities when a bulky benzhydryl substituent was present at C2 of the oxazolone (Scheme 33.8).

Several research groups have developed Michael reactions with different heterocycles that contains an easily enolizable position. For example, Melchiorre



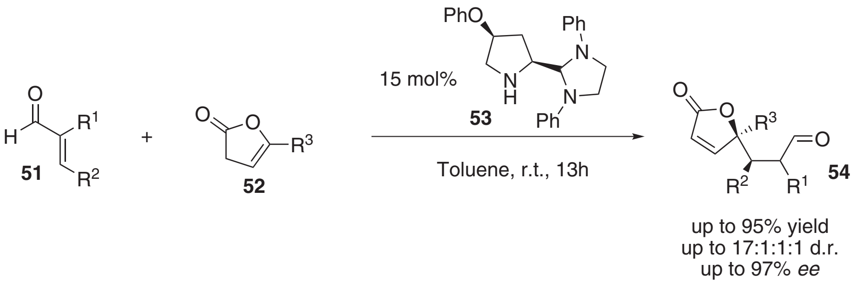
Scheme 33.8 Oxazolone addition to enals.

developed a highly enantio- and diastereoselective oxindoles addition to enals, using a primary amine bearing a thiourea moiety as catalyst (**35**) [29]. One limitation of this reaction was the need to use aromatic enals; when aliphatic enals were used the products were obtained in low stereoselectivities. To overcome this limitation, Rios and coworkers developed a similar reaction by using diphenylprolinol TMS ether (**27**) as catalyst [30]. The reaction with aliphatic aldehydes renders the final products in good yields and enantioselectivities, albeit with low diastereoselectivities (Scheme 33.9). Both groups, based on this approach, developed several cascade reactions leading to spiro-compounds [31].



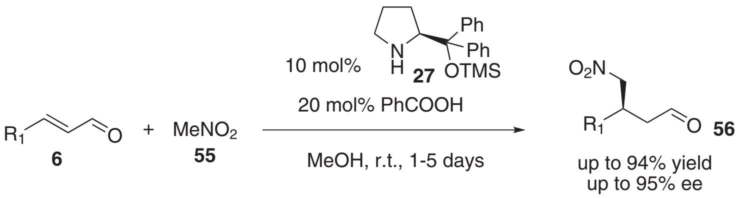
Scheme 33.9 Oxindole addition to enals.

Similar reactions were later reported by Alexakis [32] and Xue [33]. Alexakis reported the addition of γ-butenolides to enals catalyzed by proline derived catalyst **53**. In both cases, the results were excellent. The only limitation of Xue's methodology was the low enantioselectivity observed when aliphatic enals were used (Scheme 33.10).



Scheme 33.10 Addition of butenolides to enals.

Another key reaction for the addition of carbon nucleophiles to enals was reported by Wei Wang [34] and Hayashi in 2007 [35]. Hayashi developed the addition of nitromethane to enals catalyzed by **27**. The reaction renders the final γ-nitro-aldehydes in excellent yields and enantioselectivities with aromatic and aliphatic enals. At almost the same time Ye and coworkers reported the same reaction with slightly different reaction conditions (Scheme 33.11) [36]. The only limitation of the cited methodologies was the poor diastereoselectivities obtained when nitroalkanes other than nitromethane were reacted. Remarkably, these methodologies allow the synthesis of baclofen (a potent GABAβ receptor agonist) or pregabalin in enantiopure form in a few chemical steps.

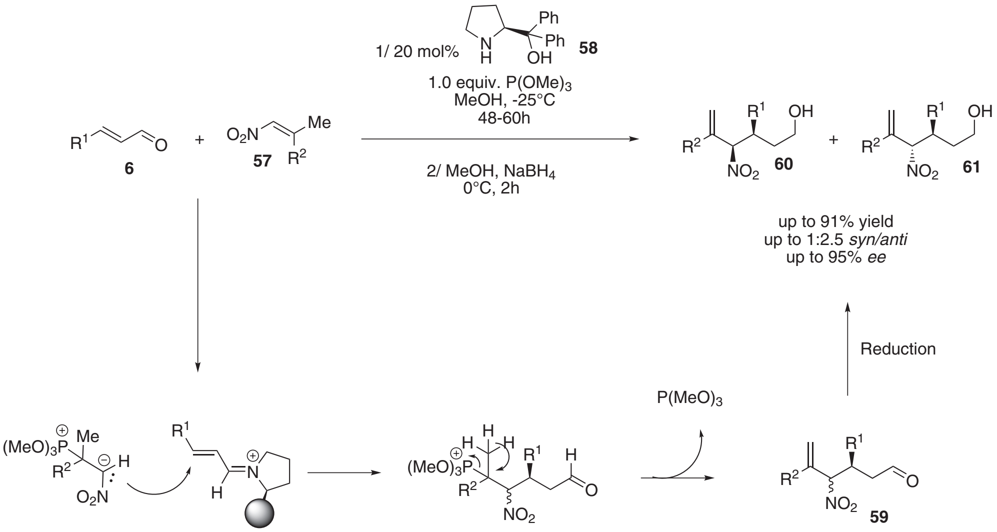


Scheme 33.11 Nitromethane addition to enals reported by Hayashi.

Based on these pioneering reports, several groups have developed cascade reactions using as a key step the addition of nitroalkane derivatives to enals [37].

Shi *et al.* developed an efficient cross double Michael addition between nitroalkenes and enals catalyzed by **58** and trimethyl phosphite via a dual activation pathway as shown in Scheme 33.12 [38]. The corresponding products were obtained in good yields and enantioselectivities, albeit with low diastereoselectivities.

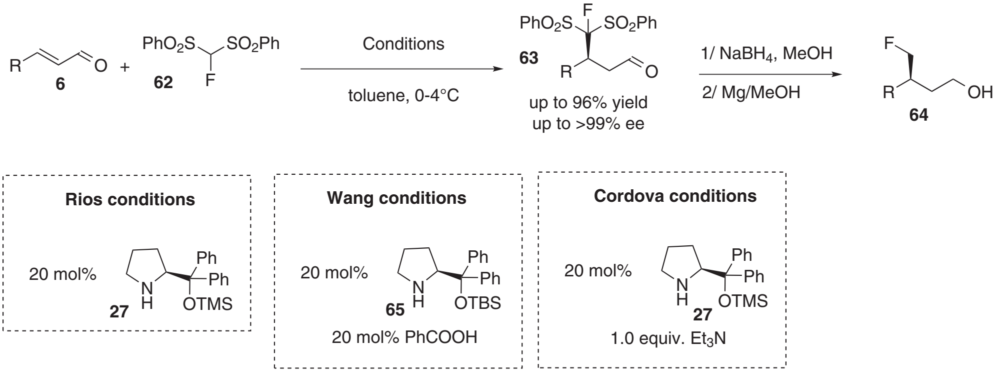
Later, Cid and Ruano reported that aryl-acetonitriles bearing an electron-withdrawing group at the *ortho-* or *para*-position could serve as suitable nucleophiles in organocatalytic Michael reactions with enals [39]. The reaction proceeded with good yields and good enantioselectivities, albeit with low



Scheme 33.12 Shi's cross double Michael addition.

diastereoselectivities. Remarkably, these adducts were transformed into diastereomerically pure lactones by a sequential procedure consisting of Michael addition, NaBH$_4$ reduction, and lactonization. A similar approach was reported by Melchiorre using nitrobenzylpyridines, obtaining similar results [40].

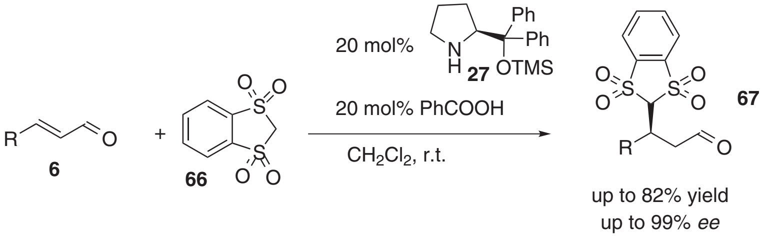
Rios [41], Wang [42], and Cordova [43] developed independently, almost at the same time, the formal fluoromethyl addition to enals. The authors took advantage of the easy removal of the bis-sulfonyl moiety. As shown in Scheme 33.13, the reaction between fluoro-bis(phenylsulfonyl)methane (FBSM, **62**) and enals (**6**) was efficiently catalyzed by **27** and the results in terms of yield and enantioselectivities



Scheme 33.13 Formal fluoromethylation of enals.

were excellent. In addition, the removal of the bis-sulfonyl moiety was performed with Mg/MeOH, furnishing the fluoromethylated products **64** in excellent yields and without any loss of enantioselectivity.

Soon after this, the research groups of Alemán [44], Rios [45], and Palomo [46] reported, almost at the same time, the first formal methyl addition to enals. Alemán and Rios used bis(phenylsulfonyl)methane as nucleophile while Palomo used a more active cyclic *gem*-bis(sulfone) (**66**). In the first two works, the reaction was limited to aliphatic enals, while the methodology reported by Palomo allows the use of both aliphatic or aromatic enals. In all the cases, the results in terms of yield and enantioselectivity were excellent (Scheme 33.14).



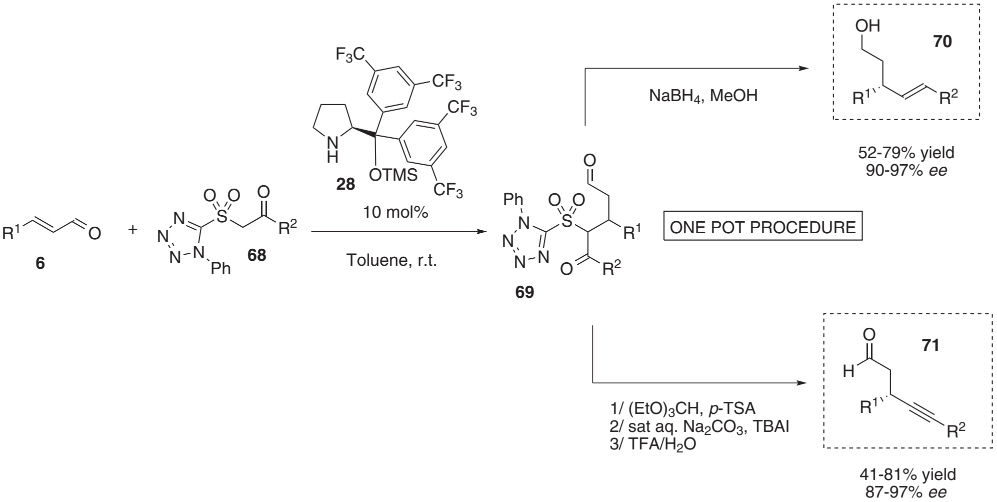
Scheme 33.14 Formal methylation of enals reported by Palomo.

Several other groups have used similar reactions, employing different sulfone derivatives. For example, Rios and Vesely developed the 1-fluoro-1-nitrophenylsulfonylmethane addition to enals [47], promoted by catalyst **27**. The final adducts were obtained in good yields and enantioselectivities but low diastereoselectivities.

Jørgensen and coworkers published an unprecedented organocatalytic protocol for the formal alkynylation and alkenylation of enals using β-keto heterocyclic sulfones [48]. The first step is, in both reactions, the Michael addition of β-keto heterocyclic sulfones to enals. The best results were obtained employing β-keto phenyltetrazole sulfones **68** as the Michael donor with diarylprolinol TMS ether (**28**) as catalyst in toluene at room temperature. Next, the Michael intermediate can be transformed into either alkynylated or alkenylated products by means of Smiles rearrangement in a simple one-pot protocol. This protocol gives access to highly enantioenriched compounds maintaining untouched the highly valuable carbonyl moiety, in contrast to the classical Julia–Kocienski transformation (Scheme 33.15).

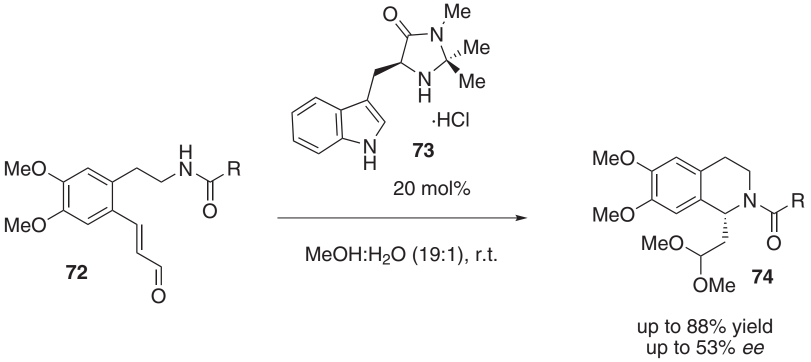
33.2.2.2 **C–N Bond Formation**

The enantioselective aza-Michael [49] reaction of enals has been emerged as one of the most important methodologies for the synthesis of enantiomerically pure C–N bonds. These methodologies led to the enantioselective synthesis of N-heterocyclic compounds such as pyrrolidines and piperidines.



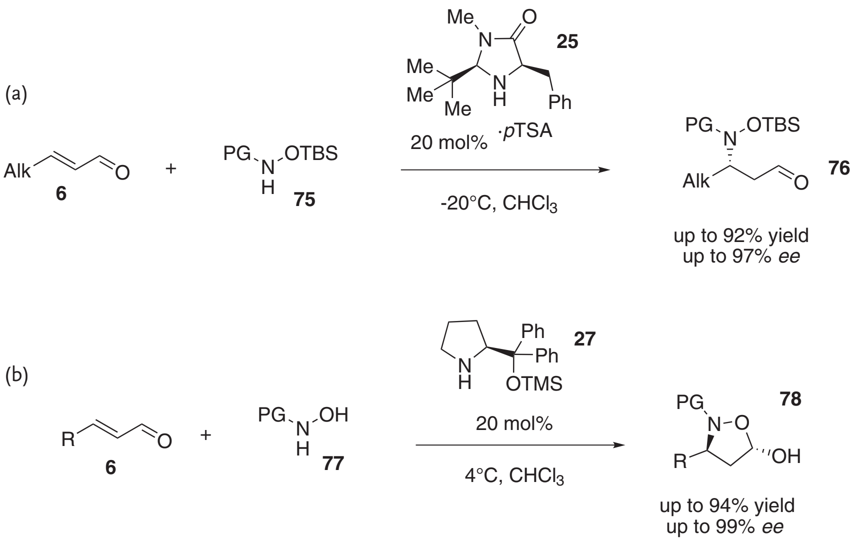
Scheme 33.15 Michael reaction reported by Jørgensen.

The first example of the aza-Michael reaction with enals was reported by Takasu and Ihara in 2003 [50]. They described the intramolecular aza-Michael reaction of dopamine derivatives bearing an enal and amide moiety catalyzed by imidazoline **73**. The reaction gives access to various 1,2,3,4-tetrahydroisoquinolines in good yields but with low enantioselectivities (Scheme 33.16).



Scheme 33.16 First organocatalytic aza-Michael reaction reported by Ihara.

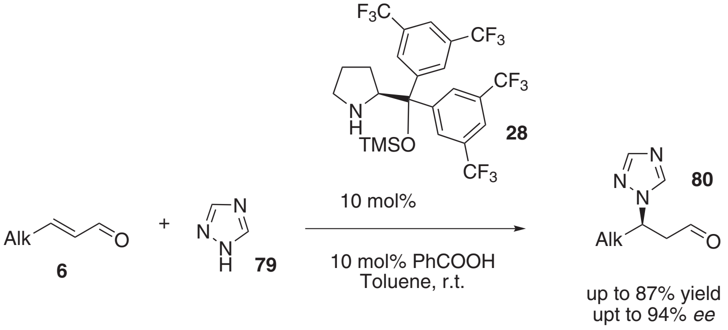
Despite this early success, it was not until 2006 that MacMillan reported the first highly enantioselective intermolecular aza-Michael addition to enals [51]. In this work, MacMillan reported the use of *N*-silyloxycarbamates as nucleophiles. The N–O functionality would increase the nucleophilicity at the nitrogen center via the α-effect, while the carbamate functionality would decrease the basicity of the nitrogen in the final product, avoiding the reverse Michael reaction. The reaction was efficiently catalyzed by imidazoline catalyst **25**, affording the final compounds in good yields and excellent enantioselectivities. However, one limitation remains unsolved: aromatic enals are not reactive under these reaction conditions. To overcome this limitation, Cordova and coworkers proposed the use of OH free *N*-hydroxycarbamates [52]. In this case, subsequent cyclization of the Michael adduct forming the cyclic hemiacetal is the driving force that pushes the reaction to the final products. Thus, this enhancement of reactivity allows the use of aromatic enals, rendering the cyclic products in excellent yields and enantioselectivities (Scheme 33.17).



Scheme 33.17 Aza-Michael reaction reported by (a) MacMillan and (b) Cordova.

In 2007, the research groups of Cordova [53] and Jørgensen [54] reported almost simultaneously the addition of different nitrogen nucleophiles such as carbamate protected methoxyamines, phthalimides, or succinimides to enals catalyzed by diaryl prolinol derivatives. In both cases, excellent yields and enantioselectivities were obtained, but again the reaction was limited to aliphatic enals. Only phthalimide reacted with cinnamaldehyde derivatives, affording the final product in moderate yields but low enantioselectivities. Interestingly, in 2009, Lee and coworkers reported the same reactions, catalyzed this time by a chiral sulfonyl hydrazine (camphor derived), leading to the aminated compounds in similar yields and enantioselectivities [55]. Remarkably, several research groups have also developed cascade reactions based on the aza-Michael reaction. For example, Cordova developed an aza-Michael–aldol cascade reaction to afford dihydroquinolines [56] and Jørgensen developed a *syn*-diamination of enals [54]. In both cases the results were excellent.

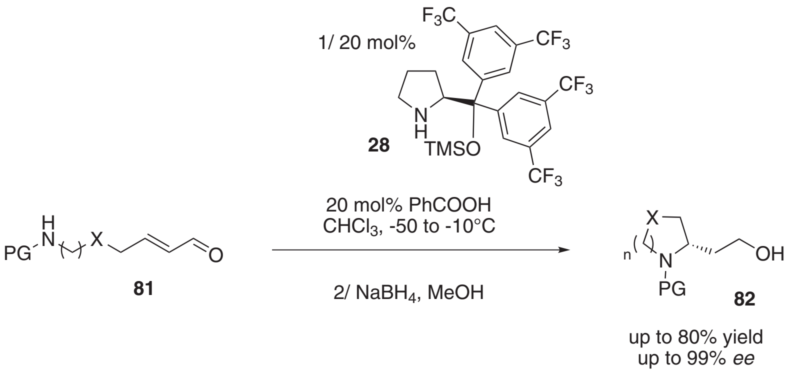
In 2007, Jørgensen and Vicario reported independently the addition of nitrogen heterocycles to enals. Jørgensen [57] reported the addition of 1,2,4-triazoles and 5-phenyltriazoles to enals catalyzed by diarylprolinol derivative **28** in excellent yields and enantioselectivities. However, in the case of 5-phenyltriazole the final adducts underwent racemization at room temperature and had to be subsequently reduced and esterified *in situ* to achieve high to excellent enantioselectivities. When benzotriazoles or 1,2,3-triazoles were added to enals a mixture of two regioisomers were obtained in acceptable yields and high enantioselectivities (Scheme 33.18). Vicario [58] reported the addition of phenyltetrazoles to aliphatic enals promoted by imidazoline catalysts. The reaction required low temperatures and renders the final compounds in good yields and enantioselectivities.



Scheme 33.18 Triazole addition of enals reported by Jørgensen.

Probably inspired by those two reports, Lin reported in 2009 a synthesis of INCB018424 (Janus kinase's inhibitor) based on an enantioselective aza-Michael reaction with an enal [59].

Based on the previous reports of Ihara, Fustero reported the synthesis of (+)-sedamine, (+)-allosedamine, and (+)-coniine via an intramolecular aza-Michael reaction using diarylprolinol derivative **28** as catalyst [60]. This methodology could be applied to the synthesis of pyrrolidine or piperidine derivatives with excellent yields and enantioselectivities. The same group studied the scope of the reaction by synthesizing (+)-myrtine, (−)-lupinine, and (+)-epiquinamide [61]. At almost the same time, Carter and coworkers independently reported a similar methodology using slightly different reaction conditions for the synthesis of enantioenriched pyrrolidine, piperidine, and indoline derivatives [62]. In contrast to Fustero's conditions, no acid additive was required. Later, Fustero expanded the scope of his reaction to the synthesis of indolines, isoindolines, tetrahydroisoquinolines, and tetrahydroquinolines using the same protocol. Moreover, he applied this methodology to the total synthesis of the alkaloid (+)-angusterine (Scheme 33.19) [63].



Scheme 33.19 Intramolecular aza-Michael reaction reported by Fustero.

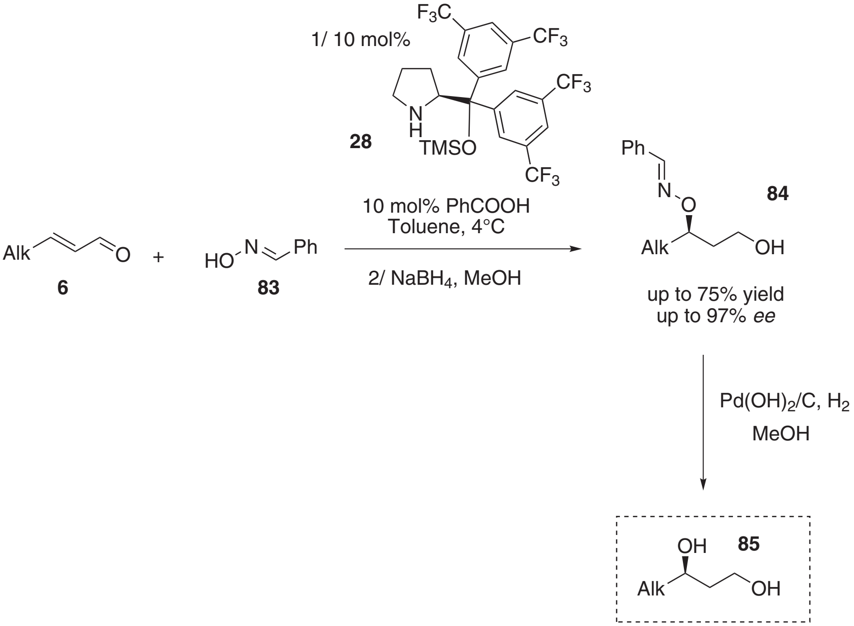
33.2.2.3 C–O Bond Formation

In contrast to the C–C Michael reactions or aza-Michael reaction the oxa-Michael reaction [64] has received considerably less attention from the synthetic community. The major drawbacks of the oxa-Michael reaction are the reversibility of the alcohol addition step as well as the poor nucleophilicity of the alcohols. Despite this fact, the oxa-Michael reaction is a very attractive methodology for the synthesis of valuable intermediates in organic synthesis like β-oxoacids, β-hydroxyketones, or β-aminoalcohols that can be found in a plethora of natural products. The organocatalytic oxa-Michael reaction with enals has been an elusive goal for organic chemists, despite the early success of Lloyd as early as 1878 in the addition of an alcohol to a conjugate acceptor. There are only few simple oxa-Michael additions of enals reported in the literature. Most of the research effort of the chemical community has gone into the development of tandem reactions that avoid the reversibility of the oxygen addition, and offer an efficient access to oxygen-containing heterocycles such as tetrahydropyrans and chromenes.

However, despite success in several tandem reactions, or in epoxidation reactions, there are only a few examples in the literature of simple oxo-Michael reactions with enals.

The first organocatalytic oxo-Michael addition to enals was reported by Jørgensen in 2007 [65]. Jørgensen used as a suitable nucleophile benzaldehyde oxime, which reacts with enals with catalysis by **28.** The resulting product, reduced directly to the alcohol due its liability, was obtained in excellent yields and enantioselectivities (Scheme 33.20). The oxime moiety can easily be cleaved to afford the 1,3-diols without loss of enantiomeric purity. However, aromatic enals turned out to be unreactive in this transformation.

In the same year, Maruoka and coworkers developed an alternative for the Michael addition of alcohols [66]. Using a biphenyl catalyst derivative, methanol, ethanol, and allylic alcohol react with aliphatic enals, albeit with moderate yields and enantioselectivities.



Scheme 33.20 Oxa-Michael reaction reported by Jørgensen.

33.2.2.4 **C–S Bond Formation**

One of the first reported C–S organocatalytic bond formations was reported by Pracejus in 1977. In this pioneering work benzylthiol, α-phthalimidomethacrylate, and catalytic amounts of chiral amines reacted to form several cysteine derivatives. With the advent of organocatalysis and iminium catalysis, several sulfa-Michael reactions have been developed.

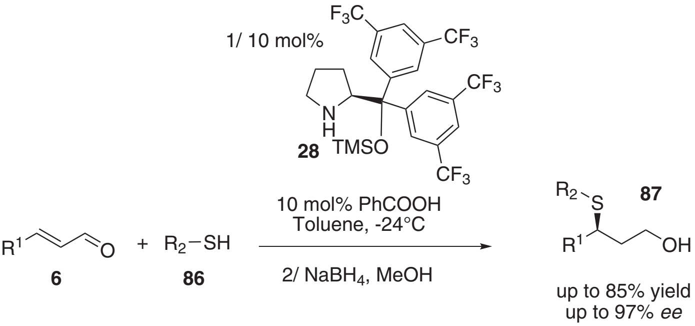
The first organocatalytic sulfa-Michael reaction of enals was reported by Jørgensen in 2005 [68]. In this report aliphatic and aromatic aldehydes reacted with several thiols in good yields and enantioselectivities under catalysis of **28.** The products must be reduced immediately due to their fast epimerization at room temperature (Scheme 33.21). In this work, Jørgensen and coworkers also developed several multicomponent cascade reactions with good to excellent results.

Since then, and inspired by this pioneering report, several groups have developed organocatalytic cascade reactions starting with a sulfa-Michael addition [68, 69].

33.2.2.5 **C–P Bond Formation**

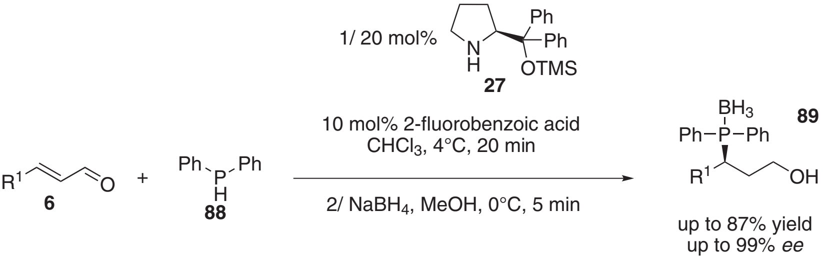
The phospha-Michael [70] additions are one of the most important methods for the enantioselective construction of C–P bonds.

The first report regarding phospha-Michael additions to enals was made independently and at the same time by the research groups of Melchiorre [71] and



Scheme 33.21 Sulfa-Michael reaction reported by Jørgensen.

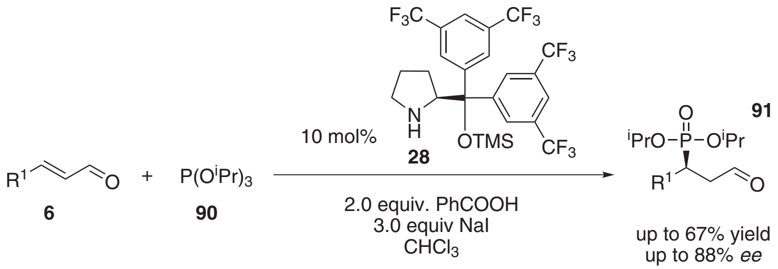
Cordova [72] in 2007. Both groups reported a hydrophosphination of enals with diphenylphosphine (**88**) catalyzed by diarylprolinol derivatives **27** (Scheme 33.22). The reactions were performed in the presence of benzoic acid derivatives as co-catalyst, and the originally formed adducts were either reduced to alcohols, which are stable and easier to handle, or oxidized to obtain the phosphine oxide derivatives. In both cases the reaction afforded the phosphine derivatives in good yields and enantioselectivities.



Scheme 33.22 Phosphination reported Cordova.

Jørgensen and coworkers reported in the same year a β-phosphonylation of enals by trialkyl phosphites [73]. The key to this reaction was the right choice of nucleophilic additive enabling the P^{III} to P^{V} oxidation by means of a S_N2-type dealkylation reaction. The optimum reaction conditions employed an excess of benzoic acid and NaI and triisopropyl phosphite (**90**) as a phosphonylation reagent under diphenylprolinol catalysis. Under these conditions the reaction afforded the final products **91** in good yields and excellent enantioselectivities (Scheme 33.23).

In 2008, Cordova expanded the scope of the previous reported reaction using different tri- or pentavalent phosphorous nucleophiles [72b]. However, the Michael adducts were formed in low yields and enantioselectivities in the best of the cases.



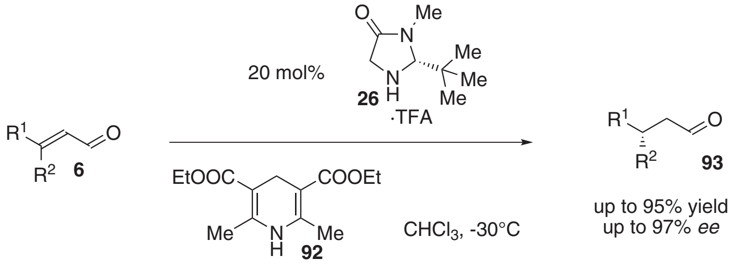
Scheme 33.23 Addition of phosphites to enals.

33.2.2.6 **C–H Bond Formation**

The asymmetric organocatalytic enantioselective conjugate hydrogen transfer reaction is clearly inspired by the mode of action in biological processes, in which reductions are accomplished by enzymes using hydride reduction cofactors like NADH.

Based on this biological approach, the research group of MacMillan [11] and List [74] reported at the same time the reduction of enals catalyzed by chiral imidazolines **26**. In both cases the key to success is the use of Hantzsch ester (**92**) as reducing agent. The Hantzsch ester can transfer simultaneously a hydride and a proton to the enal in a 1,4-addition process.

The reaction was performed with a wide range of enals, achieving in almost all the examples excellent yields and enantioselectivities (Scheme 33.24).



Scheme 33.24 Transfer hydrogenation of enals reported by MacMillan.

One important feature of this reaction is the enantioconvergence of the reaction. The reaction allowed the use of (*E*/*Z*) mixtures of the starting enal to furnish equally high enantioselectivities.

However, these two procedures have an important limitation, the low enantioselectivities obtained when β,β-dialiphatic enals were used. To overcome this limitation, List and coworkers applied the ACDC (asymmetric counterion direct catalysis) concept to this reaction [14]. When an achiral amine and a chiral phosphoric acid were used together as a catalytic system for this reaction, β,β-dialiphatic enals were reduced with good yields and exceptional levels of enantiocontrol.

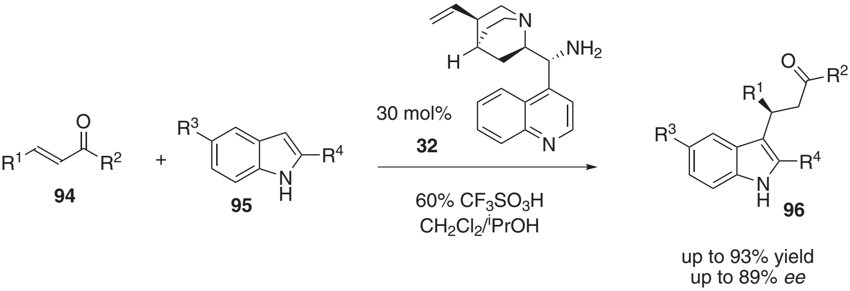
Since then, several research groups have developed several cascade and tandem reactions based on this concept [75].

33.2.3
Scope of the Nucleophilic Addition to α,β-Unsaturated Ketones

33.2.3.1 C–C Bond Formation

33.2.3.1.1 Conjugate Friedel–Craft Alkylation

Chen and coworkers in 2007 reported the first conjugate addition of indoles to enones catalyzed by 9-amino-9-deoxy-epi-cinchonine (**32**) CF_3SO_2H salts (a primary amine derived from cinchona alkaloids) [76]. The reaction proceeds with aliphatic and aromatic ketones with moderate to excellent yields and moderate to good enantioselectivities (Scheme 33.25). Soon after this, Melchiorre and coworkers reported a similar system using a hydroquinine derivative [77].



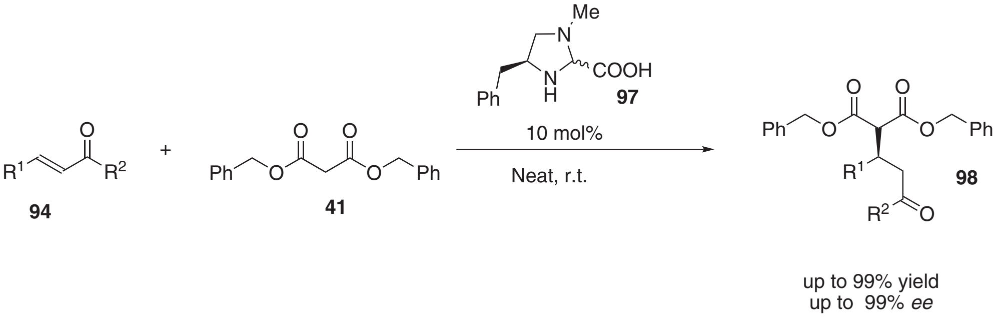
Scheme 33.25 Conjugate Friedel–Craft reaction.

33.2.3.1.2 Michael Reaction of Compounds with Acidic C–H Bond

Probably the most important organocatalytic addition to α,β-unsaturated ketones is the synthesis of the Wieland–Miescher ketone. This bicyclic diketone is obtained by a Robinson annulation consisting of a first Michael addition to vinyl methyl ketone followed by an intramolecular aldol reaction.

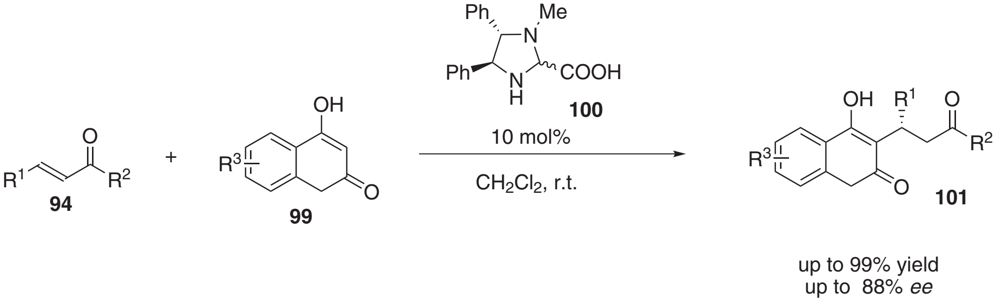
The first organocatalytic enantioselective nucleophilic addition to α,β-unsaturated ketones was reported by Kawara and Taguchi in 1994 [9]. In this report they stated that chiral proline-derived ammonium hydroxides catalyzed the reaction between malonates and α,β-unsaturated ketones in good yields and moderate enantioselectivities (up to 71%).

The next step in the organocatalytic nucleophilic addition to α,β-unsaturated ketones was made by Jørgensen and coworkers in 2003 [78]. In this report, Jørgensen reported that phenyl alanine derived catalysts (**97**) promote the addition of malonates to acyclic enones. The products (**98**) were obtained in good yields and selectivities when dibenzyl malonate (**41**) was used. However, with aliphatic or more sterically demanding enones the yields dropped significantly (Scheme 33.26).



Scheme 33.26 Malonate addition to enones reported by Jørgensen.

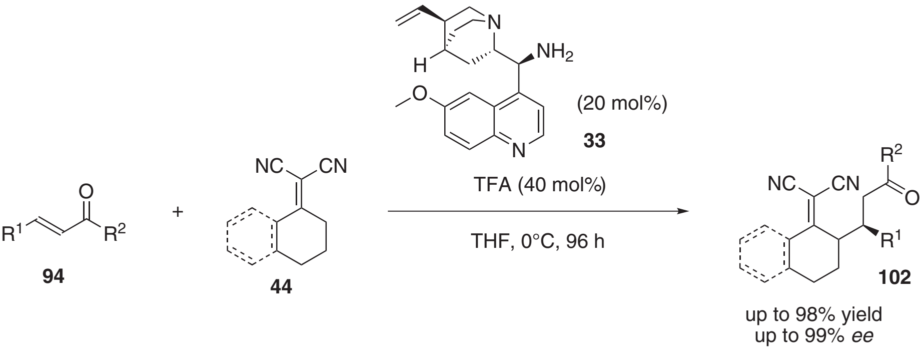
Next, the same research group expanded the scope of the reaction using cyclic 1,3-dicarbonyl compounds (4-hydroxycoumarin, **99**) [79]. This time the authors used catalyst **100**, which renders the final compounds **101** in good yields and good enantioselectivities (Scheme 33.27). However, the catalytic intermediate was not clear due to the stereochemical outcome of the reaction. Later, Chin and coworkers suggested that the catalyst decomposes under the reaction conditions to form the diamine, which could explain the facial selectivity observed.



Scheme 33.27 Jørgensen's addition of 4-hydroxycoumarin to enones.

Ley and coworkers reported in 2006 the use of the tetrazole analog of proline (**29**) in the conjugate addition of methyl or ethyl malonates to enones [80]. The reaction only needs a slight excess of the nucleophile and furnishes the final products in good yields and enantioselectivities.

In 2007, the research groups of Chen and Deng [81] applied the primary amine derived from quinine as an outstanding catalyst for the addition of different nucleophiles to enones. Chen and Deng tested this catalyst in the conjugate addition of dicyanoolefins (**44**) to enones with excellent results (Scheme 33.28). Chen [82] then

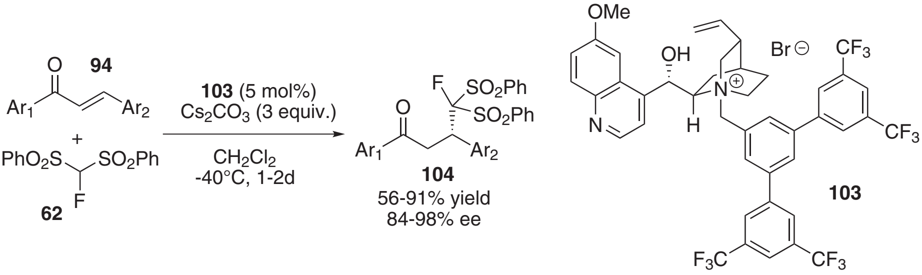


Scheme 33.28 Conjugate addition of dicyanoolefins to enones.

showed the high performance of this catalyst in the addition of 4-hydroxycoumarin to β-substituted enones with excellent results. In all these examples, the use of a strong acid as co-catalyst (usually TFA) is required. A similar reaction was reported by Feng in 2009, leading to the synthesis of warfarin using *C*2 symmetry diamines [83].

Recently, other research groups have developed the addition of 1,3 dicarbonyl or related compounds to enones. For example, Lattanzi reported the addition of malononitriles to enones catalyzed by cinchona alkaloids with good yields and enantioselectivities [84], Jaszay reported the addition of diethylcyanomethyl phosphonate to enones using thiourea catalysts with moderate yields and enantioselectivities [85], and Wang reported the Michael addition of ketones to chalcones using pyrrolidine-derived catalysts with good yields and excellent enantioselectivities [86].

To obtain a formal β-fluoromethylation of ketones, Shibata, Toru, and coworkers employed FBSM (**62**) as Michael donor in the enantioselective conjugated addition to α,β-unsaturated ketones [87]. The reaction was catalyzed by a quaternary salt derived from cinchona alkaloid (**103**), affording the final products **104** in high yields (up to 91%) and excellent enantioselectivities (Scheme 33.29).



Scheme 33.29 Enantioselective Michael addition of **62** to enones.

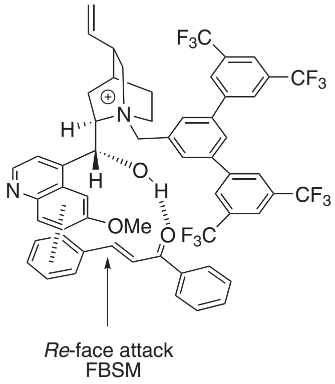


Figure 33.8 A proposed transition state assembly.

Several ammonium salts derived from cinchona alkaloids were screened as possible catalysts. Catalyst bearing the hydroxyl group methylated failed, revealing the importance of the free hydroxyl moiety in the catalyst, as well as sterically demanding benzyl substituents in the quaternary nitrogen. Thus, the quinidinium bromide catalyst (**103**) in combination with Cs_2CO_3, rendered the best results. Although only 5 mol% of catalyst was necessary, 3 equivalents of the inorganic base were necessary to achieve high enantiocontrol.

A series of chalcone derivatives and enolizable enones were reacted, affording the Michael adducts with excellent results. Finally, to obtain the fluoromethylated compound, the authors proposed a short sequence of three steps, consisting of reduction of the carbonyl moiety, reductive desulfonylation using Mg/MeOH, and oxidation with PCC. Desulfonylated products were obtained without racemization.

To justify the high enantiocontrol observed in this conjugated addition, the authors postulated a transition-state structure in which the free hydroxyl group captures the enone, presumably by hydrogen bond formation with the carbonyl oxygen atom (Figure 33.8). Aromatic π–π interaction between the enone's arylic rings and the aromatic "wings" of the catalyst additionally stabilize the transition-state structure, in which the catalyst blocks the *Si* face of the enone. Then, nucleophilic FBSM (**62**) conjugated attack through the *Re* face renders the desired product in high enantioselectivity.

In 2010, Xie reported a vinylogous Michael addition of 3-cyano-4-methylcoumarins to α,β-unsaturated ketones using primary amine catalysts derived from cinchona alkaloids to promote the reaction. The final compounds were afforded in good yields and good enantioselectivities [88].

2-Oxindoles and benzofuranones have been used as nucleophiles in the Michael addition to cyclic enones using as a catalyst primary amines derived from cinchona alkaloids [89]. The reaction afforded the final compounds in good yields and enantioselectivities but with moderate diastereoselectivities.

Another important reaction by which to form C–C bonds is the nitroalkane Michael addition. The first attempt to obtain a nitroalkane enantioselective addition to enones was reported by Yamaguchi in 1994, using as a catalyst rubinate salts of proline. The first truly enantioselective organocatalytic addition of nitroalkanes to enones was developed by Hanessian using proline as catalyst in the presence of an amine additive. The reaction affords good yields and enantioselectivities when cyclic enones were used (up to 93% ee); however, the addition to chalcones renders the products in lower enantioselectivities (up to 68% ee) [90].

Jørgensen and coworkers reported in 2002 an organocatalytic addition of nitroalkanes to acyclic β-substituted enones catalyzed by a chiral diamine [91]. The products were obtained in good yields and enantioselectivities, with the limitation that heteroaromatic, aliphatic, or bulky substituted ketones render only moderate yields. When prochiral nitroalkanes were used the diastereoselectivity was very low in all the examples. Three years later the same research group reported the use of a tetrazole derivative for the same reaction [92]. The yields and enantioselectivities were similar but the reaction times were halved. However, the limitation regarding the low diastereoselectivity obtained when prochiral nitroalkanes were used remained unsolved.

At almost the same time, Ley and coworkers reported the use of tetrazole proline catalyst for the addition of nitroalkanes to enones [93]. As in Hanessian's example, this protocol requires the use of an amine additive. In this case, the enantioselectivities obtained were excellent, albeit with moderate yields.

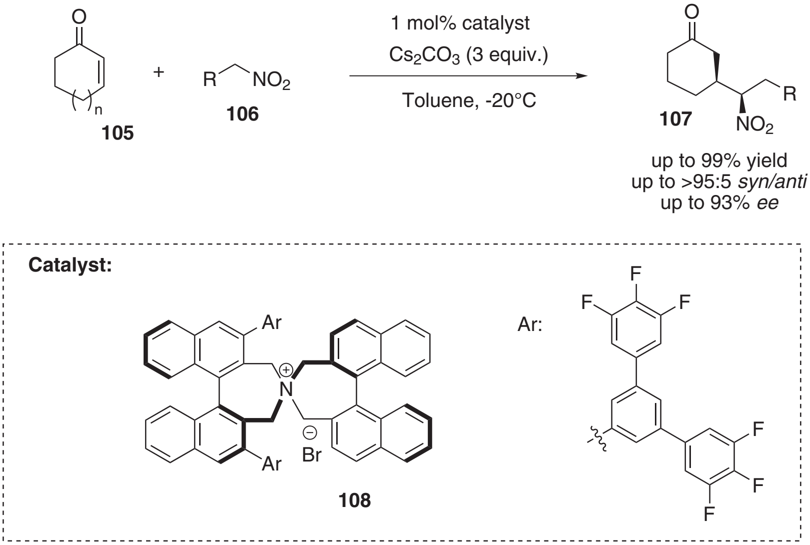
Other catalysts used in this reaction were published by Tsogoeva [94] (small peptides), Hanessian (4,5-methano-L-proline) [95], Zhao (primary–secondary amine catalysts) [96] with similar results.

In 2010, Du reported the use of chiral squaramides as catalyst for the Michel addition of nitroalkanes to chalcones with excellent results in terms of yields and enantioselectivities [97]. However, when cyclic enones were used the enantioselectivity dropped dramatically and when prochiral nitroalkanes were used the diastereoselectivity was very low.

To overcome the low diastereoselectivities reported in the Michael addition of prochiral nitroalkanes to enones, Maruoka and coworkers reported the use *N*-spiro quaternary ammonium salt (**108**) as phase-transfer catalysts [98a]. As shown in Scheme 33.30, the results in terms of yields and diastereo- and enantioselectivities were excellent. A year later, the same research group expanded the scope of the reaction with the use of silylnitronates instead of nitroalkanes [98b].

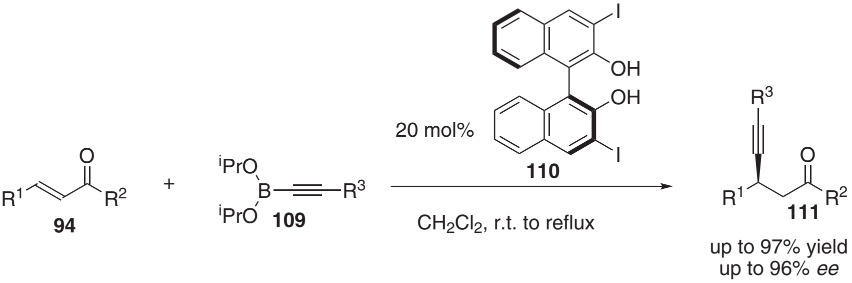
33.2.3.1.3 **Other Michael Reactions Leading to C–C Bonds**

An intriguing methodology for the organocatalytic asymmetric Michael addition of alkynyl borates to enones was reported by Chong in 2005 [99]. In this methodology BINOL derivatives are used as a catalyst and constitutes an example of a



Scheme 33.30 Addition of nitroalkanes to enones reported by Maruoka.

ligand-accelerated asymmetric process. The achiral starting boronate has a much slower rate than the BINOL-boronate. The proposed reaction is illustrated in Scheme 33.31. Achiral boronate **109** could undergo transesterification with a chiral BINOL (**110**) to form a chiral boronate, which might undergo reaction with enone and then transesterification occurred again to free the chiral BINOL. The reaction afforded the final alkynylated compounds in good yields and good enantioselectivities.

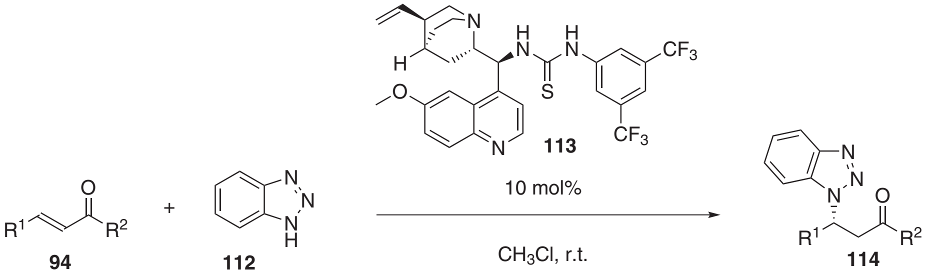


Scheme 33.31 Michael addition of alkynyl borates.

In 2009, Takemoto and coworkers reported an expansion of the scope of the above reaction, using alkenylboronic acids as nucleophiles and chiral thioureas as catalysts [100]. To activate the alkenylboronic acid a hydroxyl group at the β position was added to the enone. The thiourea activated the enone while the β-hydroxyl of the enone and the hydroxyl of the catalyst activate and direct the intramolecular attack of the alkenylboronic ester, leading to the β-alkenylated enones in excellent yields and enantioselectivities.

33.2.3.2 C–N Bond Formation

In 2007, Wang and coworkers reported the 1*H*-benzotriazole (**112**) addition to enones catalyzed by a chiral thiourea derived from cinchona alkaloids (**113**). The final products **114** were obtained in good yields but modest enantioselectivities (up to 64% ee) (Scheme 33.32) [101]. Two years later the same research group improved these results by using as catalyst a primary amine derived from cinchona alkaloids and L-*N*-Boc-phenylglycine as an additive [102]. The enantioselectivities increased up to 88% enantioselective excess. Remarkably, the authors observed the formation of the isomeric N2-addition products with high enantioselectivities but low yields.



up to 85% yield
up to 63% *ee*

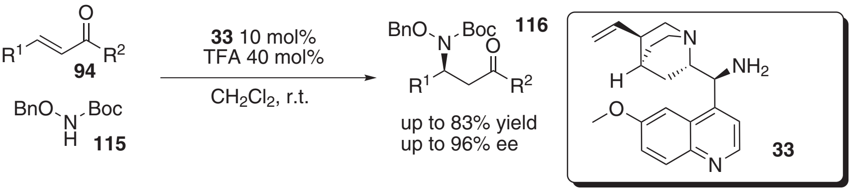
Scheme 33.32 Amination of enones reported by Wang.

At almost the same time, Ricci and coworkers reported an asymmetric aza-Michael addition of *O*-benzylhydroxyamines to chalcones catalyzed by a thiourea derived from cinchona alkaloids. The amine derivatives were obtained in good yields but low enantioselectivities (up to 60% ee) [103]. Interestingly, the thiourea moiety has a major role in the catalyst activity. When alkaloids lacking the thiourea moiety were used the reaction resulted in very poor conversions.

The same year, Jørgensen and coworkers reported an enantioselective aza-Michael addition to enones using hydrazones as nucleophiles and cinchona alkaloids as catalyst [104]. This base-catalyzed reaction renders the final aminated products in good yields but only moderate enantioselectivities (up to 77% ee).

Scettri and Acocella have reported a similar base-catalyzed reaction under solvent-free conditions using simple anilines as nitrogen source [105]. The products were obtained in excellent yields albeit with poor enantioselectivities (up to 56% ee).

In 2008, Deng and coworker developed the first highly enantioselective aza-Michael reaction to enones [106]. In this work they used 9-amino cinchona alkaloid **33** as catalyst and TFA as additive. The reaction between Boc-protected *N*-benzylhydroxylamine (**115**) and enones under these conditions renders the final products in moderate to good yields and excellent enantioselectivities. Remarkably, as was already stated by MacMillan in his aza-Michael reaction with enals, the α-effect on the oxygen linked to the nitrogen is crucial in enhancing the nucleophilicity of the nitrogen (Scheme 33.33).



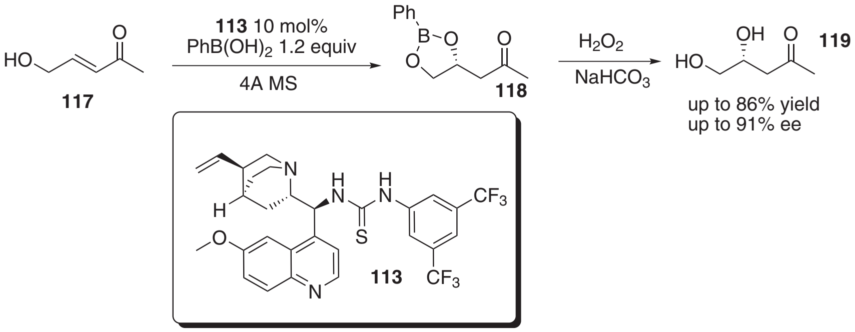
Scheme 33.33 Aza-Michael reaction developed by Deng.

A similar reaction was reported by Melchiorre [107]. Inspired by the hydroxylamine addition to enals developed by Cordova, Melchiorre reported the use of the same nucleophiles with enones catalyzed by primary amine catalysts. The results in terms of yield and enantioselectivities were excellent in almost all the examples.

Zhao and coworkers reported the use of 2-pyrazolin-5-ones as suitable nitrogen nucleophiles for the Michael reaction with enones [108]. In this report the use of 32 mol% of 9-epi-9-amino-9-deoxyquinine and 40 mol% of benzoic acid was necessary to obtain high yields and enantioselectivities.

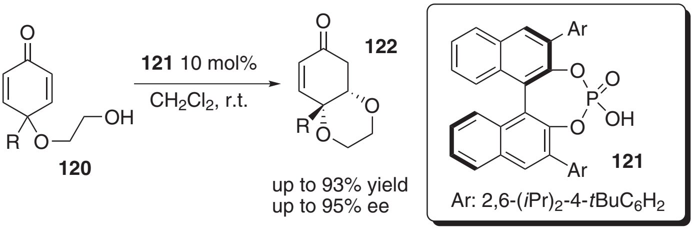
33.2.3.3 **C–O Bond Formation**

The first enantioselective organocatalytic oxo-Michael reaction to enones was reported by Falck [109]. Falck developed the intramolecular addition of boronic acids hemiesters to enones catalyzed by thiourea catalysts. Alkyl, aryl, and heteroaryl γ-hydroxy enones react with phenylboronic acid to furnish the corresponding boronic hemiesters **118**, which after oxidative cleavage of the resulting dioxaborolane renders the chiral 1,2 diols **119** in excellent yields and enantioselectivities (Scheme 33.34).



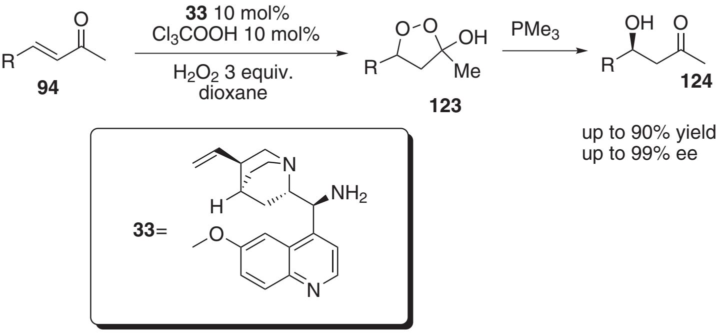
Scheme 33.34 Intramolecular addition of boronic acid hemiesters to enones.

You and coworkers developed a desymmetrization protocol based on an intramolecular oxo-Michael reaction, using as catalyst the phosphoric acid derivative **121** [110]. Cyclohexadienones **120** were transformed into the corresponding bicyclic systems **122** with high yields and enantioselectivities. Remarkably, the 4-substituent in the cyclohexadienone has a great influence on the enantioselective outcome of the reaction. Bulkier substituents at the 4-position lead to lower reaction rates and enantioselectivities (Scheme 33.35). This desymmetrization reaction was used as a key reaction for the efficient synthesis of the natural products cleroindicins C, D, and F, thereby showing the synthetic utility of this reaction.



Scheme 33.35 Desymmetrization reported by You.

List and coworkers reported an oxa-Michael reaction with aliphatic acyclic enones **94** using hydrogen peroxide as oxygen source [111]. Treatment of enones with catalytic amounts of cinchona alkaloid derived primary amine **33** (as its salt), followed by excess hydrogen peroxide furnished the intermediate peroxyhemiketals with high yields and stereoselectivities. Subsequent reduction of these compounds led to the corresponding β-hydroxyketones **124** without loss of enantioselectivity (Scheme 33.36). The same research group developed the asymmetric epoxidation of enones with excellent results [112].

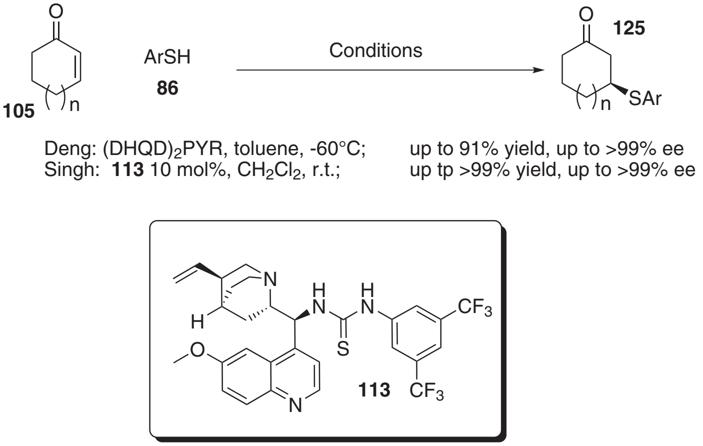


Scheme 33.36 Oxo-Michael reaction of enones reported by List.

33.2.3.4 **C–S Bond Formation**

The first asymmetric organocatalytic sulfa-Michael reaction of enones was reported by Wynberg in 1977 [113]. In this report cyclohexenone reacts with thiophenyl derivatives promoted by quinine, affording the addition products in good yields and moderate enantioselectivities. In 1981, the same research group reported the addition of thiocarboxylic acids to cyclic enones catalyzed by cinchona alkaloids, affording the thio adducts in good yields but moderate enantioselectivities.

Skarżewski reacted acyclic enones with thiols catalyzed by cinchona alkaloids [114]. Cinchonine was the best catalyst evaluated and the Michael adducts were obtained in excellent yields albeit with moderate enantioselectivities. Similar approximations were made by Mukaiyama and coworkers using hydroxyl-proline derivatives, affording the thio adducts in good yields and good enantioselectivities (up to 88% ee) [115]. However, the most effective thiol addition to enones was reported by Deng [116]. In this report $(DHQD)_2PYR$ (hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether) was used as catalysts, affording the final compounds in excellent yields and enantioselectivities (Scheme 33.37).



Deng: $(DHQD)_2PYR$, toluene, -60°C; up to 91% yield, up to >99% ee
Singh: **113** 10 mol%, CH_2Cl_2, r.t.; up tp >99% yield, up to >99% ee

Scheme 33.37 Thio-Michael reaction reported by Singh and Deng.

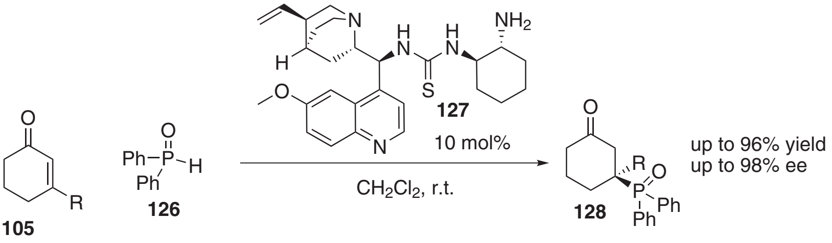
In 2006, Wang and coworkers reported the use of chiral bifunctional amine thiourea catalysts for the Michael reaction between thioacetic acid and different enones, affording products in excellent yields but moderate enantioselectivities (up to 63% ee) [117].

In 2010, Singh and coworkers reported the use of cinchona alkaloid derived urea **113** as catalyst for the Michael addition of aromatic thiols to enones [118]. The reaction renders excellent yields and enantioselectivities with aliphatic or cyclic enones, while aromatic enones afford slightly worst enantioselectivities (Scheme 33.37).

33.2.3.5 **Other Michael Reactions**

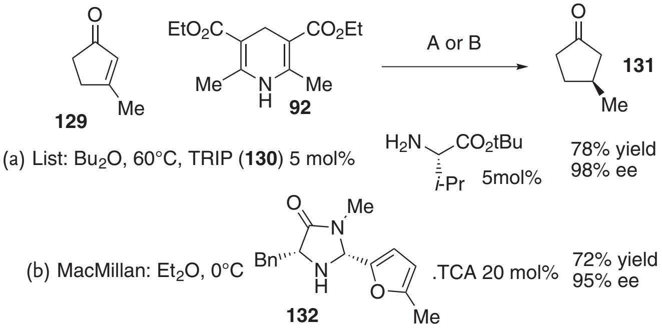
Despite the great interest in chiral phosphines and the success in the phospha-Michael addition to enals, only one example of an organocatalytic phospha-Michael reaction to enones can be found in the literature.

Ye, Liang, and coworkers reported the addition of diphenylphosphine oxide to enones catalyzed by a bifunctional primary amine thiourea catalyst (**127**) derived from cinchona alkaloid (Scheme 33.38) [119]. Cyclic and acyclic enones react with phosphine oxides under the optimized conditions to furnish the phosphine derivatives **128** in excellent yields and enantioselectivities. The primary amine of the catalyst activates the enone via an iminium, while the thiourea moiety activates and directs the phosphine group.



Scheme 33.38 Phosphination of enones reported by Ye.

In 2006, the research groups of List [120] and MacMillan [121] independently reported the organocatalytic, highly enantioselective transfer hydrogenation of enones using Hantzsch esters (**130**) as the hydrogen source. List used as catalysts primary amino esters derived from amino acids plus a chiral phosphoric acid. This combination results very effectively in the hydrogenation of cyclic enones or acyclic enones, affording the final products **131** in excellent yields and enantioselectivities. On the other hand, MacMillan used as catalyst a furyl imidazoline TCA salt (**132**). Under the optimized conditions the reaction furnishes the reduced products **131** in good yields and excellent enantioselectivities. The only limitation of MacMillan's methodology is that only cyclic enones could be used (Scheme 33.39).


129
92
A or B
131
(a) List: Bu_2O, 60°C, TRIP (130) 5 mol%
5mol%
78% yield
98% ee
(b) MacMillan: Et_2O, 0°C
.TCA 20 mol%
132
72% yield
95% ee

Scheme 33.39 Transfer hydrogenation of enones.

33.3
Conclusion

Organocatalysis have emerged recently as one of the cornerstones for the enantioselective synthesis of C–C or C–heteroatom bonds. Owing to the easy prediction of the stereochemical outcome of the reactions, iminium activation and specific Michael reactions is one of the most studied reaction types in organocatalysis. In the literature, we can find multiple approaches to the organocatalytic Michael reaction using different catalysts or nucleophiles, most of them with exceptional levels of stereoselectivity. Moreover, these simple additions to enals or enones have inspired multiple organocatalytic tandem and cascade reactions and, in our view, open up a new pathway for the enantioselective construction of complex scaffolds in one-pot procedures.

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34
Addition to Nitroolefins and Vinyl Sulfones

Christèle Roux and Cyril Bressy

34.1
Introduction

Michael addition and more generally conjugate additions to electron-deficient olefins have since the beginning of organocatalysis been a privileged field of investigation. Among the large variety of Michael acceptors, nitroolefins are probably the most used. The reasons for such interest lie in the versatility of the nitro group, which could be converted into an amino group or carbonyl group through the Nef reaction, and also in the high electrophilicity of nitroolefins [1]. During the period 2000–2007, the principal mode of activation employed the route through an enamine intermediate [2]. However, since 2003 other modes of activation such as the use of H-bonding have been explored. In comparison to nitroolefins, vinyl sulfones and vinyl selenones emerged more recently as Michael acceptor in organocatalysis with other synthetic potentialities [3, 4]. In this chapter we will focus on the diversity of the modes of activation employed in organocatalysis to reach high level of enantioselectivity with these three types of Michael acceptors. This overview is greatly dependent upon the nature of the catalysts and thus will be organized accordingly.

34.2
Addition to Nitroolefins

34.2.1
Enamine Activation

Two classes of catalysts were developed to promote enamine activation: secondary and primary amines.

34.2.1.1 Secondary Amines

The success of proline in organocatalysis guided studies to the design of catalysts based on its framework, providing a highly nucleophilic amine moiety

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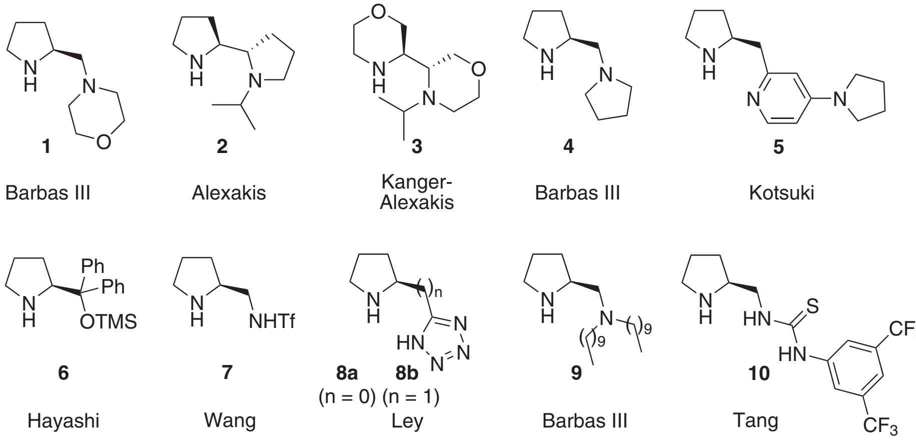


Figure 34.1 Selected organocatalysts bearing a secondary amine function.

(Figure 34.1). Nevertheless, initial studies with proline, conducted by the groups of List [5] and Enders [6], in different solvents with proline yielded poor enantioselectivities (23% and 46% ee, respectively). Diamines such as **1**, which is a proline derivative, were introduced by the group of Barbas in the same year to catalyze addition of aldehydes onto nitroolefin with good diastereo- and enantioselectivities (up to 78%) [7]. In 2002, Andrey and Alexakis described the use of bis-pyrrolidine **2** as catalyst in the Michael addition of carbonyl compounds to nitroolefins with a good degree of enantioselectivity (up to 85% ee) [8]. The authors suggested that the tertiary amine moiety acts as a shield on one face of the intermediate enamine. Later, Kanger and Alexakis modified the catalyst structure of **2** to afford bis-morpholine **3**, affording better selectivities in the addition of aldehyde to nitroolefins (ee up to 90% and dr up to 95 : 5) [9]. In 2004, Tanaka and Barbas studied the challenging addition of α,α-disubstituted aldehydes to various nitrostyrenes with the (pyrrolidinylmethyl)pyrrolidine salt **4** [10]. Good enantioselectivities (up to 86% ee) and moderate diastereoselectivities (dr up to 89 : 11) were obtained, highlighting the difficulties in controlling the geometry of enamine in this case. A high level of selectivities (ee up to 99% and dr up to 99 : 1) in a ketone series was obtained with bifunctional catalyst **5** developed by Kotsuki *et al.* [11]. In the transition state proposed by the authors, protonated pyrrolidinopyridine acts as a steric shield blocking a face of the enamine. The versatile Hayashi–Jørgensen catalyst **6** provided excellent results in the Michael addition to nitroalkenes due to the presence of the bulky diphenylsilyloxymethyl group [12]. Aldehydes could be added to β-alkyl and β-aryl nitroalkenes with exceptional ee values (99% in all cases apart from α,α-disubstituted aldehydes). More recently, catalyst **6** was also shown to be highly regioselective toward 1,4-addition using nitrodiene as electrophile [13]. Wang *et al.* developed bifunctional catalyst **7**, which is able to guide a nitroolefin with a sulfonamide arm during the approach of the enamine in a manner that makes the transition state rigid [14]. Catalyst **7** was also versatile in activating aldehydes, α,α-disubstituted aldehydes, and ketones, although limitations appeared with β-alkyl nitroolefins. A tetrazole group could also serve to stabilize the approach of nitroolefin in the transition state through hydrogen bonding. Ley's group developed two catalysts, **8a** [15] and **8b** [16], with different arm lengths between the pyrrolidine moiety and the tetrazole heterocycle. The homoproline tetrazole **8b** afforded better selectivities than **8a** with six-membered ring cyclic ketones (up to 93% ee). Michael addition of aldehydes and ketones to nitroolefins in aqueous media (brine) proceeded through enamine activation using **9**, a catalyst bearing long hydrophobic chains [17]. These aliphatic chains seem to improve the reactivity of the catalyst through better interactions between organic reagents condensed in a single phase, thereby facilitating the enamine formation. Tang *et al.* developed bifunctional organocatalyst **10** bearing a pyrrolidine moiety and a thiourea function known to chelate the nitro group [18]. Excellent results were obtained for the conjugate addition of cyclohexanone to nitroolefins (ee up to 98% and dr up to >99 : 1).

In parallel to diamines, another class of catalysts, primary amines, was developed to activate carbonyl compounds.

34.2.1.2 Primary Amines–*Anti*-Selectivity

Less studied than secondary amines in the past decade, primary amines took a growing importance more recently. Indeed the higher reactivity and the lower steric hindrance of primary amines compared to secondary amines can be helpful to promote some Michael addition. The reduction of steric demand makes possible the pathway through a (*Z*)-enamine intermediate leading to *anti*-adducts.

Several catalysts bearing a primary amine group were developed to promote the Michael addition of aldehydes and ketones to nitroolefins (Figure 34.2). Among them Xu and Cordova explored derivatives of alanine with success in terms of selectivities using the simple amide **11** [19]. Butanone gave the *syn*-adduct as major product (dr *syn* : *anti:* 5 : 1) in this study while bifunctional catalyst **12** described by Tsogoeva and Wei [20] inverted this selectivity, furnishing predominantly the *anti*-adduct (dr *syn* : *anti*: 14 : 86). The Jacobsen's group designed two catalysts, **13** [21] and **14** [22], resulting from a connection through a thiourea function between a *tert*-leucine moiety and a *trans* cyclohexyldiamine fragment. Catalyst **13**, with a tertiary amide, was able to promote the addition of various ketones onto

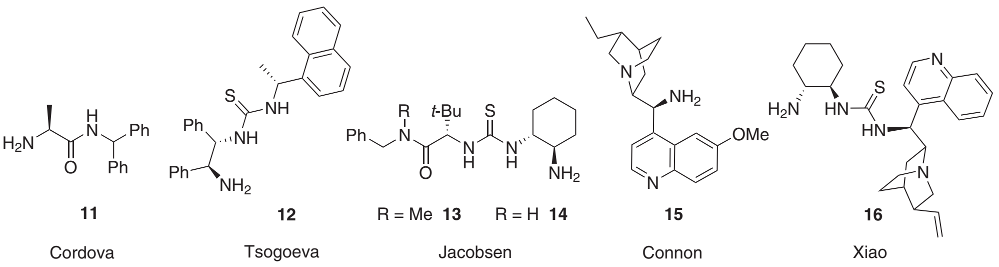
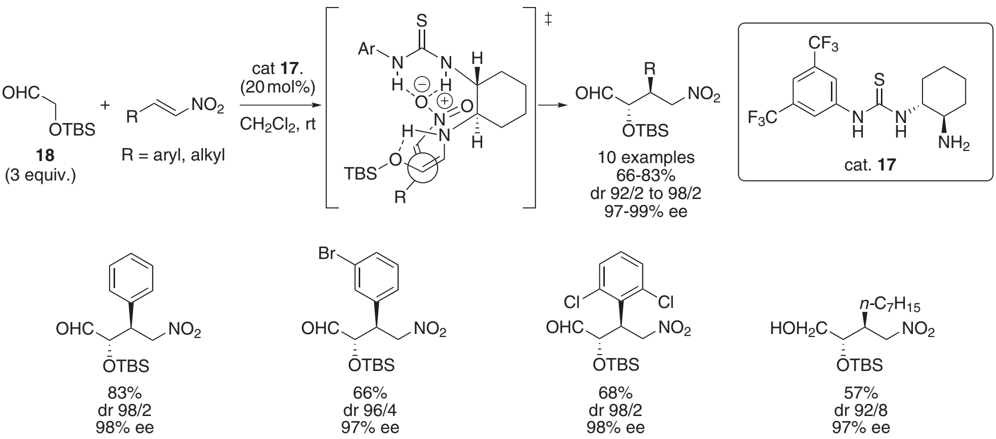


Figure 34.2 Organocatalysts bearing a primary amine employed in 1,4-conjugate addition.

nitroalkenes with high levels of enantio-, diastereo-, and regiocontrol with an *anti*-selectivity observed even with an alkyl group. Catalyst **14**, with a secondary amide, was employed for the addition of α,α-disubstituted aldehydes to generate all-carbon quaternary stereogenic centers. Impressive ee values (92–99%) were obtained on a broad scope with moderate to excellent diastereoselectivity (up to >50 : 1). McCooey and Connon employed 9-epi-aminodihydroquinine **15** as catalyst for the addition of ketones, aldehydes, and α,α-disubstituted aldehydes to nitroolefins with generally good stereocontrol and *syn*-selectivity [23]. Xiao *et al.* studied the addition of isobutyraldehyde to nitroolefins using the catalyst **16**, which is built on the quinine scaffold [24]. Excellent enantioselectivity (up to 98% ee) was observed with β-aryl nitroolefins but limitations appeared on changing the nature of the α,α-disubstituted aldehyde partner.

Fine catalyst tuning seems to play an important role in the diastereoselectivity of the Michael addition. As was shown earlier, all of the primary amines catalysts did not allow *anti*-adducts. Nevertheless, some particular partners with a heteroatom group (generally an oxygenated one) in the α-position of the carbonyl lead to the *anti*-adduct due to a H-bonding in the enamine intermediate. α-Hydroxyketones gave typically good level of diastereoselectivity in favor of the *anti*-adduct [25].

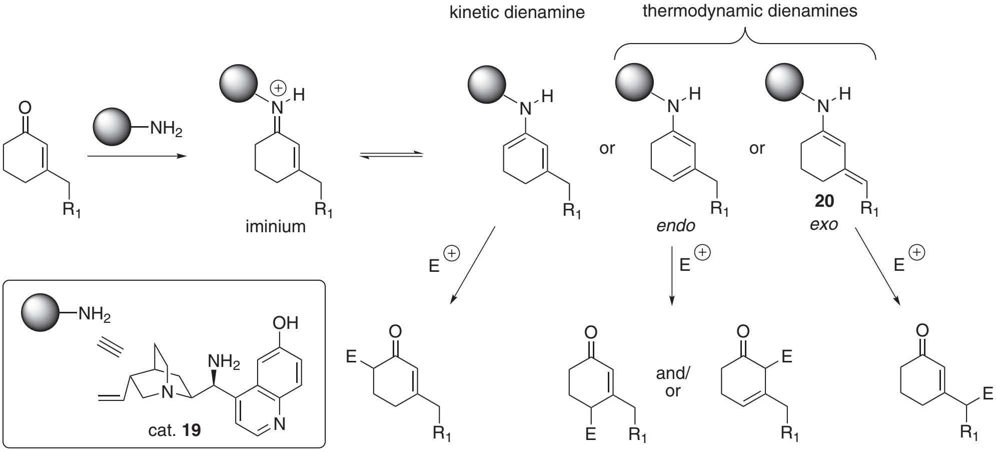
Surprisingly, such selectivity was observed only recently in an aldehyde series. Indeed the group of Barbas developed a catalyst able to perform *anti*-selective Michael addition of aldehydes [26]. To facilitate such a transformation, several parameters were adjusted to promote the formation of (*Z*)-enamine, which is necessary to obtain an *anti*-selectivity: (i) the classical secondary amine catalyst was changed for primary amine **17**, which is less sterically hindered, favoring the (*Z*)-enamine, and (ii) the substrate was chosen to be able to form a stabilizing intramolecular H-bonding in favor of the (*Z*)-enamine. For these reasons (*tert*-butyldimethylsilyloxy)acetaldehyde (**18**) was selected as pro-nucleophile. Excellent level of enantio- and diastereoselectivity were obtained on combining these both parameters (Scheme 34.1). In the postulated transition state, covalent interaction



Scheme 34.1 *Anti*-selective addition of aldehydes to nitroolefins.

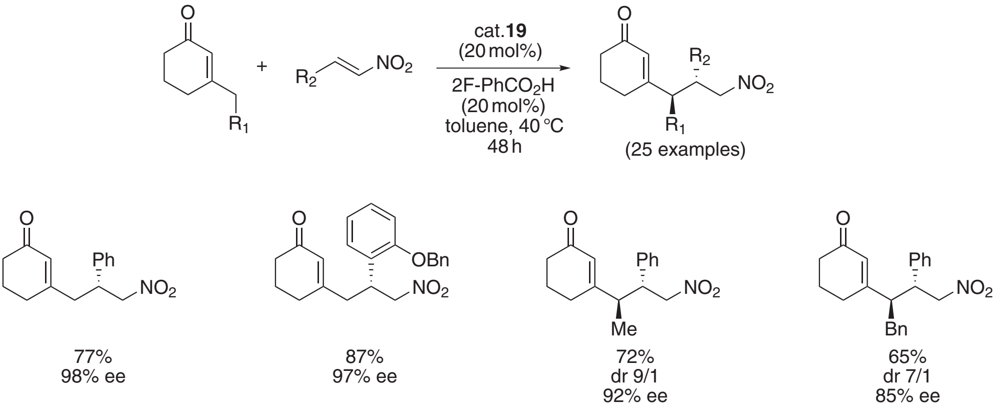
operates between aldehyde **18** and the amino moiety of the catalyst in (*Z*)-enamine form and activation of the nitroolefin with the thiourea part occurs through H-bonding. The acyclic synclinal approach is similar to Seebach's model but an additional stabilizing interaction, H-bonding between the enamine NH and the oxygen atom of the OTBS group, is proposed to explain the diastereoselectivity.

The group of Melchiorre expanded the nature of donors to γ-enolizable enones [27], usually considered in organocatalysis as electrophiles, using dienamine activation. Indeed β-substituted cyclohexenones were activated by chiral primary amine **19** derived from cinchona alkaloid to become a dienamine nucleophilic species that could react with nitroolefins. Among the three dienamines that could be formed after iminium generation (Scheme 34.2), the conditions described by Melchiorre *et al.* selectively favored thermodynamically the *exo* dienamine **20.**



Scheme 34.2 Possible functionalizations of γ-enolizable enone by dienamine activation.

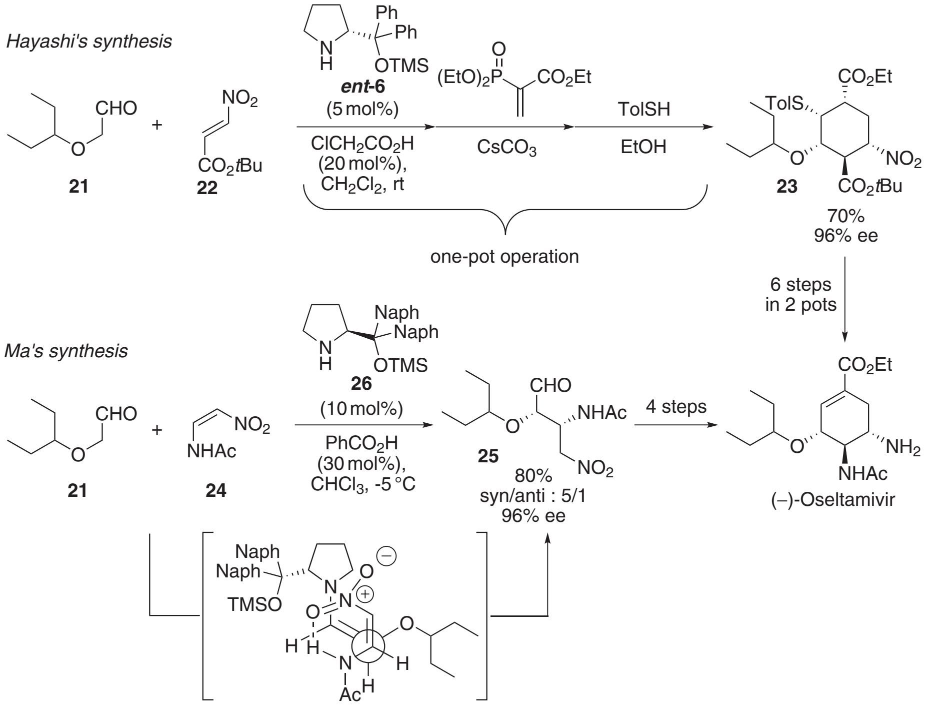
Highly enantioselective conjugate additions (98% > ee > 85%) were performed under primary amine **19** catalysis, providing products with two contiguous stereogenic centers (if R^1 is different from a hydrogen atom) with a high level of diastereoselectivity (13.5 : 1 > dr > 2 : 1) (Scheme 34.3). The authors suggested that the carboxylic acid co-catalyst favored the iminium–dienamine equilibrium leading predominantly to the thermodynamically stable *exo* intermediate **20.**



Scheme 34.3 Organocatalyzed conjugate addition of cyclohexenone to nitroolefins.

34.2.1.3 **Applications in Total Synthesis**

(−)-Oseltamivir is a relevant synthetic target that in recent years has encouraged organic chemists to develop efficient pathways towards it. Two groups employed conjugate addition on nitroolefins to obtain this anti-flu drug. First, Hayashi *et al.* [28] began their synthetic sequence with the diphenylprolinol silyl ether **6** catalyzed conjugate addition of aldehyde **21** to *tert*-butyl (*E*)-β-nitroacrylate **22** (Scheme 34.4).



Scheme 34.4 Hayashi's and Ma's syntheses of (−)-oseltamivir.

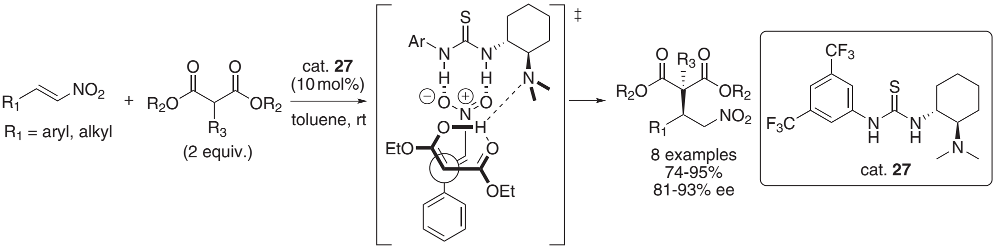
The adduct was not isolated but included in a one-pot reaction featuring a nitro-Michael/Horner–Wadsworth–Emmons olefination domino reaction followed by a thio-Michael addition to reach the densely functionalized cyclohexane **23.** Two other one-pot reactions including six different operations were necessary to furnish (–)-oseltamivir. The enantioselective organocatalyzed addition of aldehydes to such nitroacrylates in water was studied in by the group of Ma [29]. These authors [30] also focused their attention on obtaining (–)-oseltamivir but starting from (*Z*)-2-nitroethenacetamide **24** and the same aldehyde **21** as Hayashi's synthesis. Using partner **24,** the synthetic sequence was drastically reduced since only four steps after the formation of adduct **25** were necessary to reach (–)-oseltamivir. Noticeably, the configurations of the two catalysts *ent*-**6** and **26** involved in each syntheses are opposite. The proposed transition state for the Michael addition in Ma's synthesis, depicted in Scheme 34.6, is unusual. Indeed it seems that there is a steric repulsive interaction between the amido group of the acceptor and the ether group of the enamine leading to a (*Z*)-configuration of this last intermediate.

34.2.2
Hydrogen Bonding Activation

On using enamine activation, nucleophiles were limited to aldehydes and ketones but the emergence of H-bonding activation [31] has expanded considerably this scope. With this mode of activation other carbon-centered nucleophiles and also heteroatom-centered nucleophiles could be considered. During the period 2003–2012, growing interest was focused on the ability to perform catalytic enantioselective reactions with small organic molecules able to produce such weak interactions.

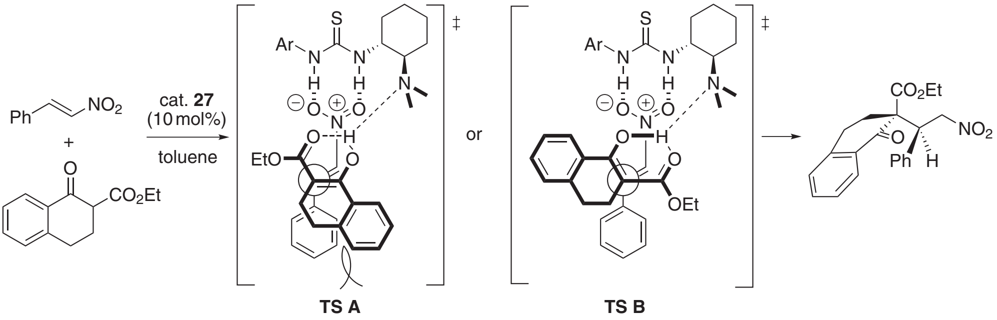
34.2.2.1 Carbon-Centered Nucleophiles

Takemoto and coworkers [32] elaborated bifunctional catalyst **27,** which was found, after this initial report, to be highly versatile in promoting a large variety of transformations. The combination of a thiourea and a tertiary amine separated by a chiral scaffold, (*R,R*)-1,2-cyclohexyldiamine, was studied to build a new type of organocatalyst. Aminothiourea **27** was first examined as catalyst for the enantioselective addition of malonate to nitroalkenes (Scheme 34.5). The thiourea moiety of catalyst **27** guides and activates the nitroolefin while the tertiary amine part deprotonates the malonate.



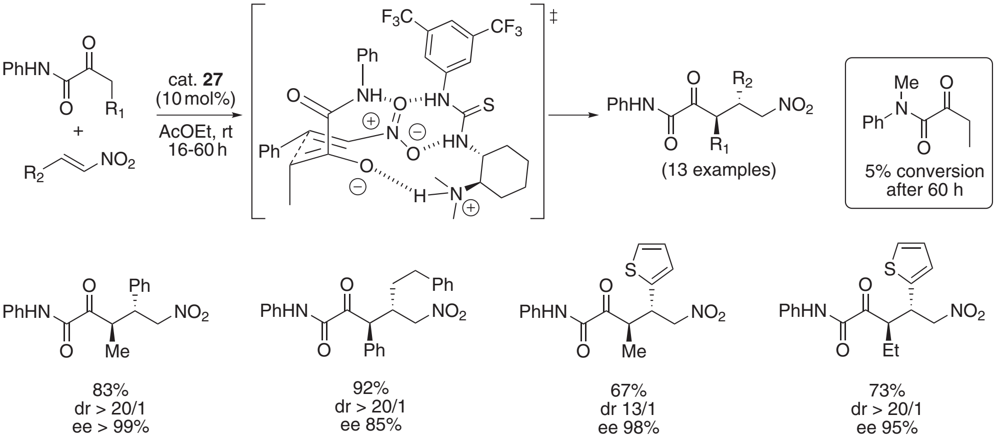
Scheme 34.5 Addition of malonates to nitroolefins catalyzed by bifunctional Takemoto's urea.

This reaction was extended with success to β-ketoesters [33], furnishing adducts with two contiguous stereogenic centers, including an all-carbon quaternary stereogenic center, still with a high enantioselectivity but also with a moderate to excellent diastereoselectivity (Scheme 34.6). The authors suggested a disfavored interaction in transition state TS A, which does not exist in TS B, to explain the observed diastereoselectivity.



Scheme 34.6 Organocatalyzed addition of β-ketoesters to nitroolefins.

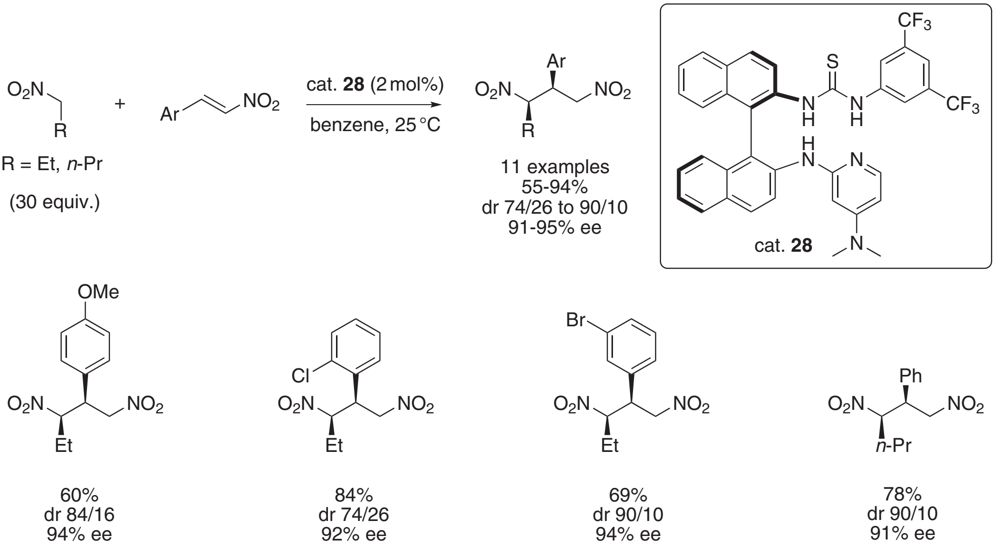
Recently, Takemoto's catalyst **27** was also employed in the addition of β-ketoamides [34] with excellent results. Bonne, Constantieux, Rodriguez *et al.* [35] reported the use of α-ketoamides as pronucleophiles in the Michael addition to nitroalkenes catalyzed by the bifunctional Takemoto's aminothiourea **27**. During this study it appeared that the nature of the amide moiety was crucial, indeed tertiary amides were poorly reactive during conjugate addition while secondary amides gave excellent results in terms of yields (67–94%), enantioselectivity (99% > ee > 85%), and diastereoselectivity (20 : 1 > dr > 10 : 1) (Scheme 34.7). The authors



Scheme 34.7 Organocatalyzed conjugate addition of α-ketoamides to nitroolefins.

suggested a transition state involving, in addition of the activation of nitro group and the *Z*-enolate stabilization by ammonium moiety, a tertiary activation by H-bonding between the NH of amide function and the nitro group rigidifying the transition state.

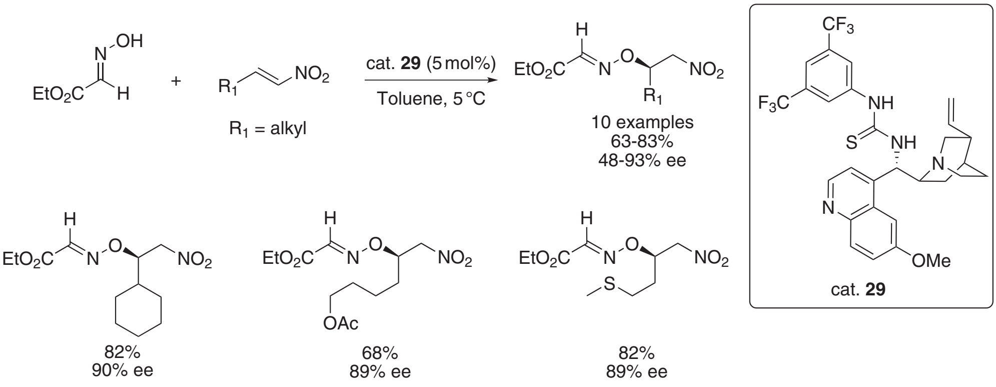
A few groups investigated the addition of nitroalkanes to nitroalkenes. One of the main contributions was accomplished by the group of Wulff [36] with the elaboration of bifunctional catalyst **28** bearing a basic DMAP (dimethylaminopyridine) and a thiourea function connected by a chiral linker based on (*R*)-2,2′-diamino-1,1′-binaphthyl. Wulff's catalyst bearing a 2-substituted DMAP moiety performs better in terms of TOF than Wang's catalyst [37] which is based on a similar framework. Nevertheless, a large excess of nitroalkanes was necessary to obtain good results. Good *syn* diastereoselectivity (74 : 26 to 90 : 10) and excellent enantioselectivity (91–95% ee) were produced (Scheme 34.8).



Scheme 34.8 Organocatalyzed conjugate addition of nitroalkanes to nitroolefins.

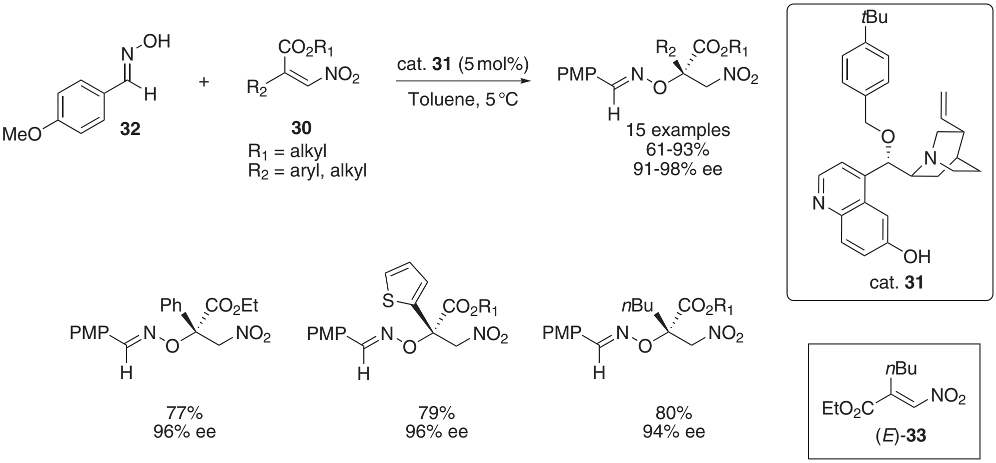
34.2.2.2 **Oxa-Michael Addition**

Oximes have been known as oxa-Michael partners in organocatalysis since the work of Jørgensen's group [38], who used α,β-unsaturated aldehydes as acceptors and iminium activation. The same group extended this addition to nitroolefins but employed bifunctional organocatalyst **29**, which activates the nitroolefin by H-bonding [39] with the thiourea moiety while the tertiary amine acts as a base with the oxime partner. An electron-deficient oxime, like ethyl glyoxylate oxime, was able to be a partner under the optimized conditions described by the authors (Scheme 34.9). The nature of the nitroalkene was limited to those bearing an alkyl group because adducts obtained from nitrostyrenes were prone to a retro-Michael reaction.



Scheme 34.9 Asymmetric conjugate addition of oximes to nitroolefins.

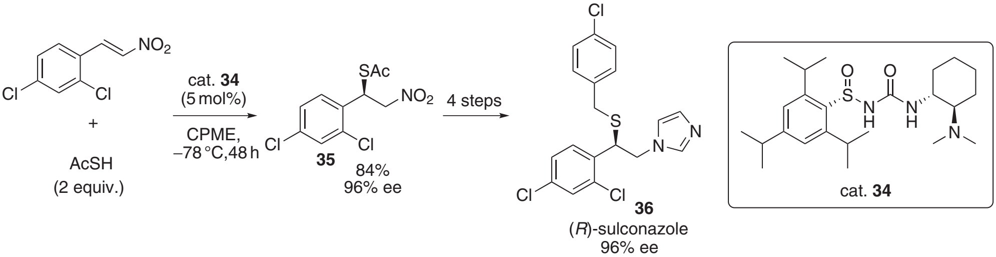
Chen, Xiao, and coworkers [40] expanded the scope of this reaction to the trisubstituted nitroacrylate (*Z*)-**30** (Scheme 34.10). They employed the derivative **31** of the cinchona alkaloid described by the group of Deng [41] as catalyst. The phenolic-OH and the quinuclidine moieties help to organize the transition state of the transformation. In contrast to Jørgensen's study, electron-rich oxime **32** was employed under these conditions. Moreover, the geometry of nitroacrylate turned out to be a crucial parameter in the course of the reaction; indeed, if nitroacrylate (*E*)-**33** was employed the adduct was isolated in only 45% yield after 4 days, and with poor enantioselectivity (7%).



Scheme 34.10 Asymmetric conjugate addition of oximes to nitroacrylates.

34.2.2.3 Sulfa-Michael Addition

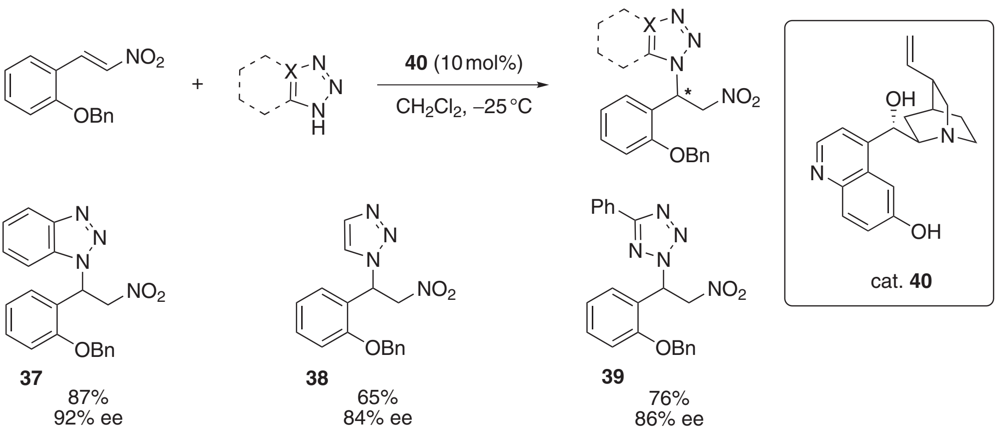
Ellman and coworkers reported quite recently the first asymmetric organocatalyzed conjugate addition to nitroalkenes using their *N*-sulfinyl ureas [42]. They identified the bifunctional organocatalyst **34** as the most selective to promote the addition of thioacetic acid to nitroolefins (nine examples, 65–95% yield, 78–96% ee). To illustrate this methodology, this group applied it to the enantioselective synthesis of (*R*)-sulconazole (**36**) which is of pharmaceutical interest (Scheme 34.11). After the asymmetric conjugate addition, adduct **35** was converted through four additional steps into (*R*)-sulconazole.



Scheme 34.11 Synthesis of (*R*)-sulconazole through organocatalyzed sulfa-Michael.

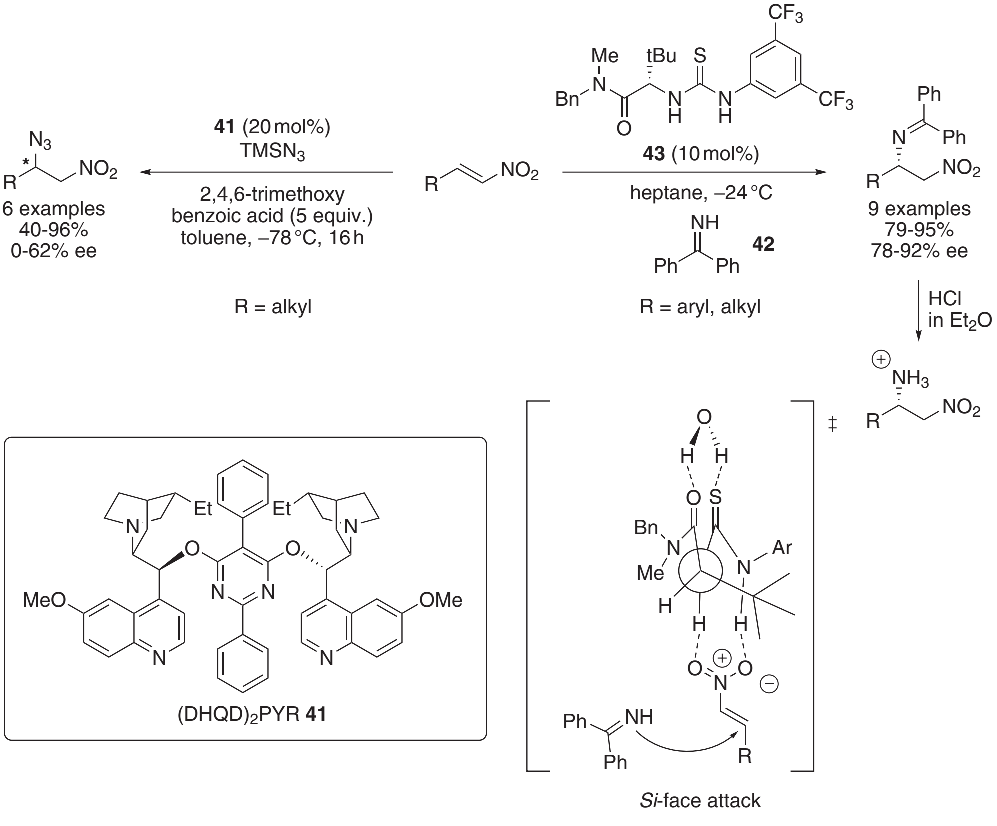
34.2.2.4 Aza-Michael Addition

The scope of the heteronucleophiles added to nitroalkenes was also extended to different nitrogen derivatives. In this direction, Wang and coworkers [43] explored the addition of N-heterocycles, such as benzotriazole **37**, 1*H*-[1,2,3]triazole **38**, and 5-phenyl-1*H*-tetrazole **39**, to various nitroolefins bearing an aryl or alkyl side-chain (Scheme 34.12). The cinchona alkaloid derivative **40**, bearing a phenolic-OH, was the most efficient in promoting this addition.



Scheme 34.12 Asymmetric conjugate of azaheterocycles on nitroolefins.

To obtain vicinal diamines, which constitute valuable building blocks in organic synthesis, the group of Jørgensen studied successively the addition of trimethylsilyl azide [44] and imine [45]. In both cases they employed cinchona alkaloid derivatives as catalysts. After optimization, $(DHQD)_2PYR$ (**41**) proved to be the most efficient catalyst even if a low level of enantioselectivity was reached with $TMSN_3$ as nucleophile (up to 62% ee, six examples) (Scheme 34.13). The initial screening of conditions had shown that acidic additives were beneficial to the selectivity of the transformation. The authors suggested a double role for this additive: firstly to generate the real nucleophile HN_3 and secondly to protonate the catalyst organizing the transition state through H-bonding. The same group explored more recently the addition of imine **42** using thiourea **43** with greater success (Scheme 34.13). Imine **42** was particularly attractive because of its facile deprotection and acted as an ammonia equivalent. The presence of water (10 mol%) did not affect the yield and the enantioselectivity of the reaction while the addition of molecular sieves dramatically lowered the ee value along with an inversion of the selectivity. Based on these results, Jørgensen *et al.* suggested the intervention

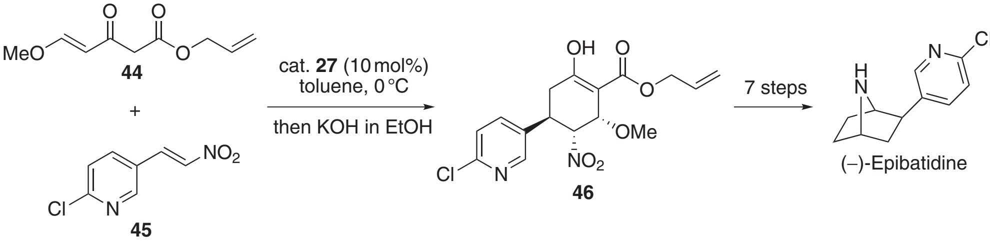


Scheme 34.13 Organocatalyzed addition of azide and imine to nitroolefins.

of a molecule of water to increase the rigidity of the transition state depicted in Scheme 34.13.

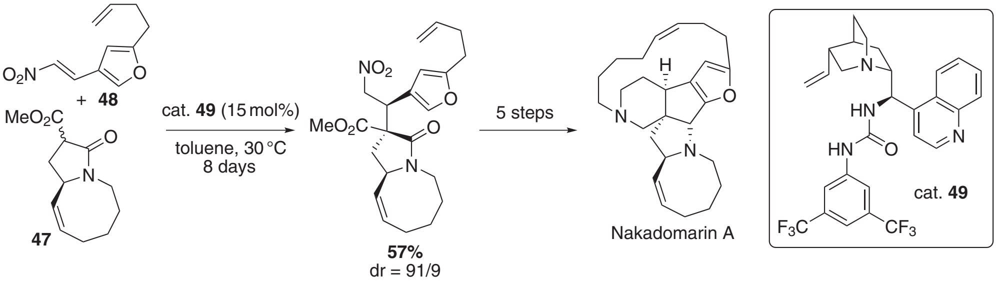
34.2.2.5 Applications in Total Synthesis

An elegant one-pot multi-bond forming reaction involving an organocatalyzed conjugate addition to nitroalkene was accomplished during Takemoto's synthesis of (–)-epibatidine (Scheme 34.14) [46]. The chiral bifunctional thiourea **27** catalyzed the asymmetric addition of β-ketoester **44** to the nitroolefin **45**, which bears the pyridine ring of the natural product. The adduct was then treated subsequently in the same pot with KOH to promote an intramolecular Michael addition on the enone moiety, forming the cyclic intermediate **46.** Complete diastereoselectivity was observed but only a moderate enantioselectivity was produced (75% ee) in this one-pot transformation.



Scheme 34.14 Total synthesis of (–)-epibatidine by Takemoto *et al.*

The diastereoselective Michael addition of β-amidoester **47** to nitroalkene **48,** catalyzed by the bifunctional urea derived from cinchona alkaloid (**49**), was one of the key-steps in the total synthesis of nakadomarin A (Scheme 34.15) reported by Dixon *et al.* [47, 48]. The same catalytic system was employed successfully in the synthesis of two anti-depressant molecules, Rolipram® and Paroxetine®, by this group [49].

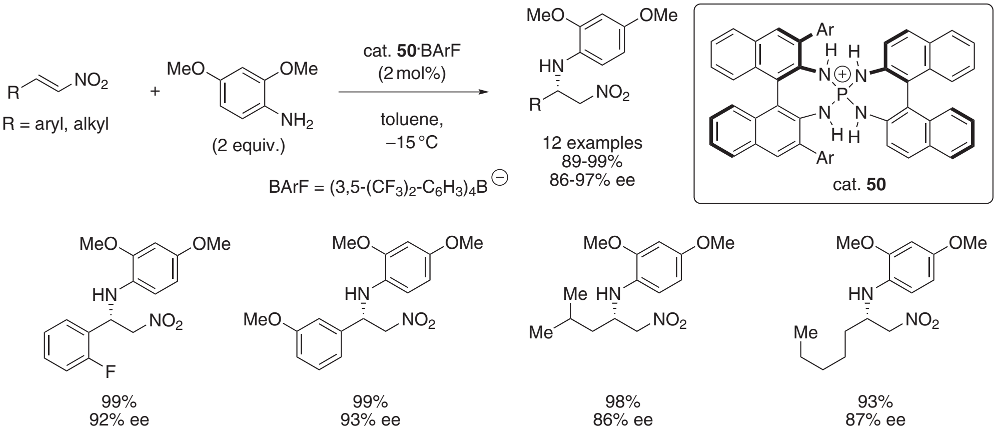


Scheme 34.15 Total synthesis of nakadomarin A by Dixon *et al.*

34.2.3

Acidic Activation

Among the few examples of pure acidic activation in Michael addition to nitroalkenes, the recent works of Ooi and coworkers described the aza-Michael addition of aniline [50] by the charged chiral C_2 symmetric phosphonium **50** (Scheme 34.16). Indeed, the acidic spirocyclic catalyst **50** was able to asymmetrically activate a Lewis base such as 2,4-dimethoxyaniline, to promote the addition to nitroolefins with excellent yields and selectivity.



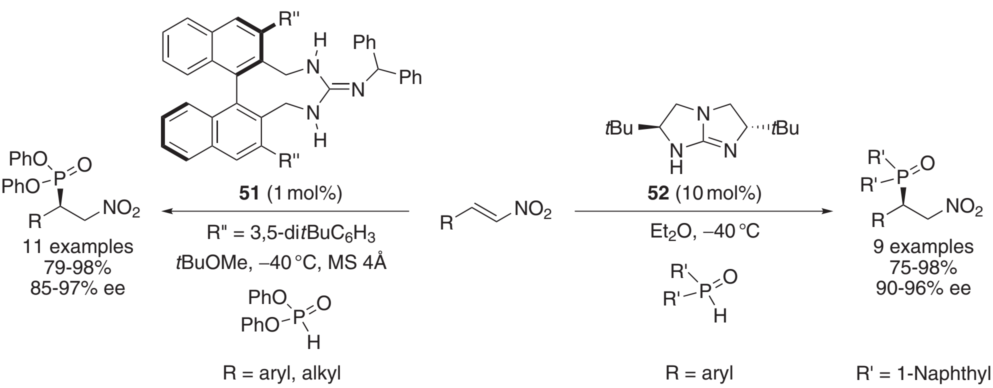
Scheme 34.16 Addition of anilines to nitroolefins promoted by an acidic organocatalyst.

34.2.4

Basic Activation

Examples of asymmetric conjugate addition to nitroolefins using chiral organic bases activation in catalytic amounts were reported in the phospha-Michael series. Independently, the groups of Terada [51] and Tan [52] studied the catalysis of chiral guanidines to promote the addition of diphenyl phosphite or diarylphosphine oxide, respectively, to nitroolefins. Terada and coworkers developed guanidine **51** bearing axial chirality while Tan employed bicyclic guanidine **52** containing two stereogenic centers (Scheme 34.17).

Tan also examined the addition onto α,β-disubstituted nitroolefins with catalyst **52** and observed excellent diastereoselectivity (>95 : 5) in favor of the *anti* adduct.

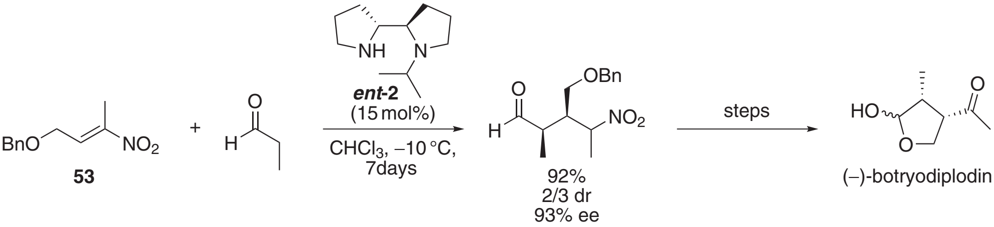


Scheme 34.17 Guanidine catalyzed phospha-Michael addition on nitroolefins.

34.2.5
Challenging Substrates

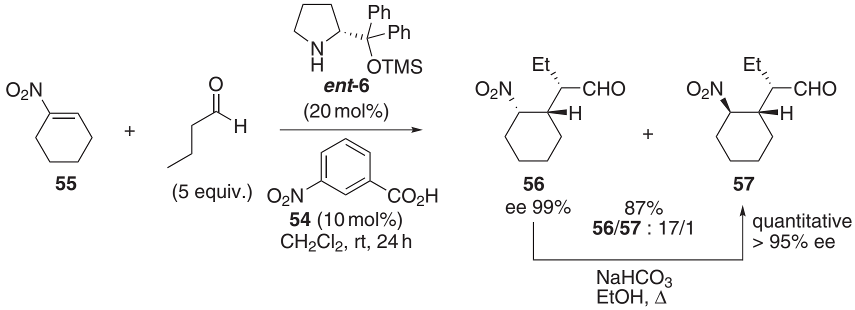
34.2.5.1 α,β-Disubstituted Nitroolefins

Probably the most challenging issue concerning asymmetric conjugate addition to nitroolefin is the control of both enantio- and diastereoselectivities with α,β-disubstituted acceptors. These Michael acceptors present a lower reactivity than the acceptor without a group at the α-position due to non-planarity increasing the steric demand and reducing the conjugation between the double bond of the nitroolefin and its aryl group in the β-position [53]. Nevertheless, this kind of transformation is very interesting in terms of providing building blocks with up to three contiguous stereogenic centers generated in a single operation. One of the first examples was reported by Alexakis *et al.* in 2003 [54] during the synthesis of (–)-botryodiplodin (Scheme 34.18). Poor diastereoselectivity (dr 2 : 3) was observed with acceptor **53** when using diamine *ent*-**2** as catalyst and a prolonged reaction time was also necessary to provide a good yield.



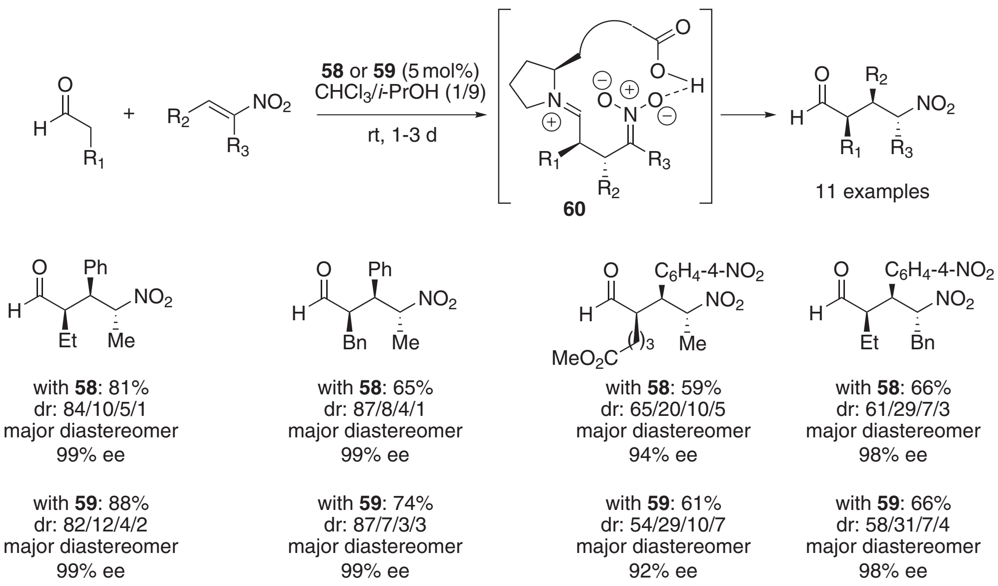
Scheme 34.18 Total synthesis of (–)-botryodiplodin.

The case of cyclic nitroolefins was first examined by Gellman *et al.* in 2009 [55] during a study *en route* to the synthesis of conformationally constrained γ-amino acids. This group found that combining chiral pyrroline *ent*-**6** and acidic additive **54** was an excellent catalytic system for the conjugate addition of aldehyde to 1-nitrocyclohexene (**55**, Scheme 34.19). The authors suggested that the role of acidic co-catalyst **54** is to facilitate hydrolysis of the iminium intermediate, thereby improving the turnover of the catalyst *ent*-**6**. The major diastereomer observed was cis adduct **56**, which could be converted into trans adduct **57** under basic conditions in quantitative yield and with slight erosion of the enantiomeric excess. The trans selectivity may be explained by a preferential equatorial reprotonation of the nitronate intermediate. Gellman *et al.* examined exclusively, in this study, the influence of aldehyde nature with 1-nitrocyclohexene (**55**), and excellent selectivities were observed in all cases (17 : 1 > dr > 8 : 1 and 99% > ee > 96%).



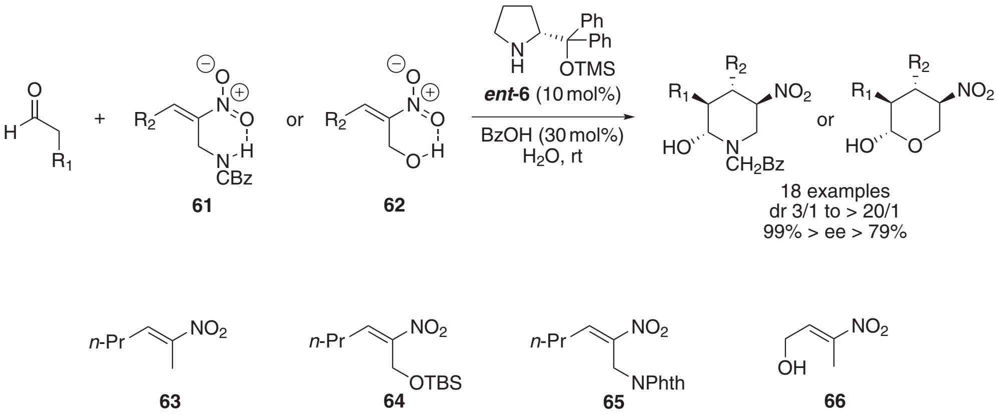
Scheme 34.19 Enantioselective conjugate addition on nitrocyclohexene.

The group of Wennemers explored the catalysis by tripeptides of the Michael addition between aldehydes and nitroalkenes [56]. The peptide H-D-Pro-Pro-Asp-NH_2 exhibited excellent performance in terms of selectivities and yields with a low catalytic loading (0.1 mol%) on a broad scope of β-substituted nitroolefins [57]. Kinetic studies [58] highlighted that both the reaction between enamine and the nitroolefin and the hydrolysis of the iminium are rate limiting. This group focused recently on the addition on α,β-disubstituted nitroolefins catalyzed by such tripeptides [53]. After screening of catalyst structures, two tripeptides, H-Pro-Pro-D-Gln-OH (**58**) and H-Pro-Pro-Asn-OH (**59**), presented a high level of diastereo- and enantioselectivities (Scheme 34.20). A rationalization was proposed that involves selective protonation of the nitronate **60** in a rigidified intermediate due to intramolecular H-bonding.



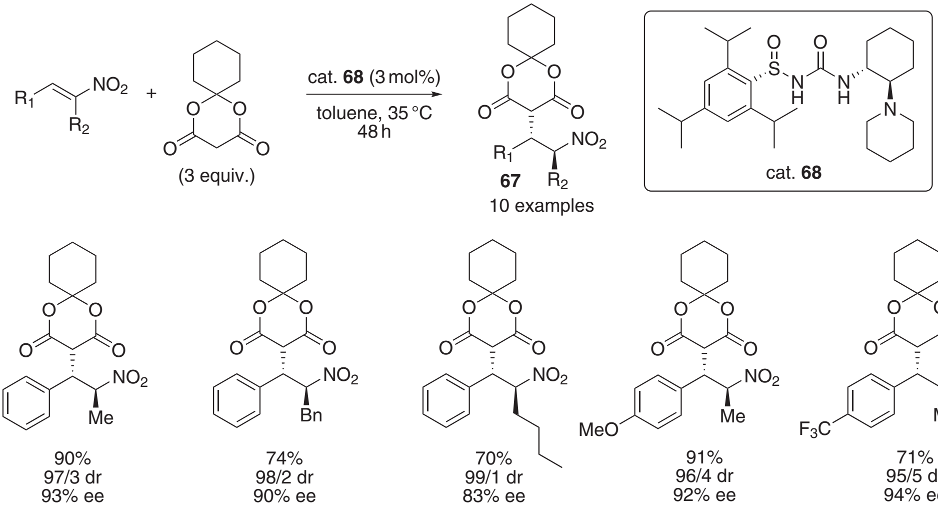
Scheme 34.20 Addition on α,β-disubstituted nitroolefins by tripeptide catalysis.

A means of activating α,β-disubstituted nitroolefins studied by Ma's group [59] employs an acceptor possessing an intramolecular hydrogen bond such as **61** or **62** (Scheme 34.21). The nitroolefins **63**–**66** without the appropriate intramolecular activation were unreactive under the same conditions.



Scheme 34.21 Organocatalyzed Michael addition on activated α,β-disubstituted nitroolefins.

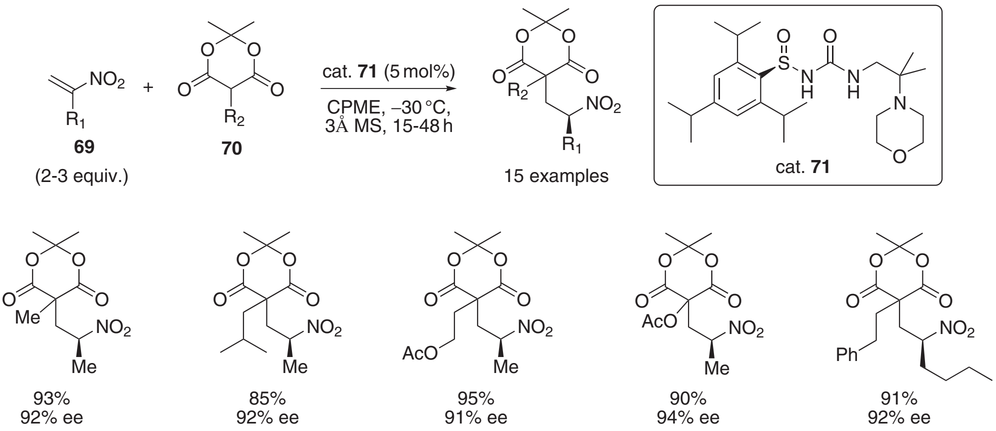
The group of Ellman described recently the highly enantioselective and diastereoselective addition of cyclohexyl Meldrum's acid to α,β-disubstituted nitroolefins, using *N*-sulfinyl ureas, to give *anti* adducts **67** [60]. Unlike Wennemers' catalyst **58**, Ellman's catalyst **68** acts through non-covalent activation. Indeed, the sulfinyl urea **68** is a bifunctional catalyst bearing a Brønsted acid moiety and a Brønsted base with a tertiary amine. This catalyst presents excellent selectivity with alkyl- or aryl-β-substituted nitroolefins (73–99% yield, 94–98% ee) under mild conditions (cyclopentyl methyl ether, room temperature, 22 h) with a low catalytic loading (1 mol%). Noticeably, on a mole scale this loading could be reduced to 0.2 mol%, which is rarely possible in organocatalysis. The most impressive performance of sulfinyl urea **68** was undoubtedly obtained when using α,β-disubstituted nitroolefins, with the same Meldrum's acid under slightly modified conditions (toluene, 35 °C, 48 h), rather than β-substituted nitroolefins (Scheme 34.22). The enantioselectivity was still excellent (83–98%) and the diastereoselectivity was also exceptional for acyclic α,β-disubstituted nitroolefins (between 95 : 5 and 99 : 1). For cyclic nitroolefins, the thermodynamic trans isomer was formed mostly, in contrast to the results described by Gellman *et al.*



Scheme 34.22 Addition of Meldrum's acid to α,β-disubstituted nitroolefins.

34.2.5.2 **Terminally Unsubstituted Nitroolefins**

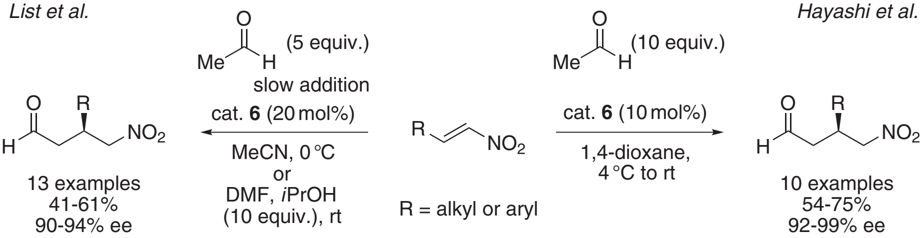
The same group investigated recently the catalysis of *N*-sulfinyl ureas in the field of terminally unsubstituted nitroolefins [61], which constitutes a previously unexamined type of acceptor when α-substituted [62]. The optimization stage went through a step of organocatalyst design that revealed that catalysis of conjugate addition between α-substituted nitroethylene **69** and α-substituted Meldrum's acids **70** could be performed with a catalyst bearing a unique stereogenic element centered on the sulfur atom. In fact, bifunctional *N*-sulfinyl urea **71** gave the best results in term of enantioselectivity (Scheme 34.23). The stereogenic center generated during this transformation results from an enantioselective protonation of the nitronate intermediate by the Meldrum's acid derivatives.



Scheme 34.23 Addition to terminally unsubstituted nitroolefins.

34.2.5.3 Acetaldehyde

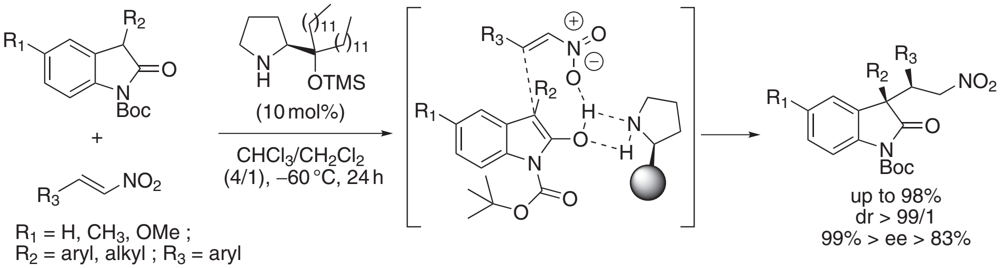
The simplest enolizable aldehyde, acetaldehyde, was until recently not examined in organocatalytic reactions due to its high reactivity as electrophile or as nucleophile leading to intractable mixture of products resulting from side reactions. The groups of List [63] and Hayashi [64] reported independently the use of acetaldehyde as donor in Michael addition to nitroalkenes (Scheme 34.24). They both selected diphenylprolinol silyl ether (**6**) as the best catalyst but employed different solvents (acetonitrile or DMF/Pr^{i}OH for List, and 1,4-dioxane for Hayashi) at room temperature. Similar selectivities were observed under both conditions but higher yields were obtained with Hayashi's conditions.



Scheme 34.24 Organocatalyzed Michael addition of acetaldehyde to nitroolefins.

34.2.6
Miscellaneous

The group of Enders recently disclosed an original use of prolinol TMS ether as organocatalyst to promote the Michael addition of oxindoles to nitroolefins (Scheme 34.25) [65]. The reaction proceed through Brønsted base activation despite the fact that such a catalyst structure, chiral pyrrolidine, was usually employed in enamine/iminium activation of aldehydes and ketones. The transformation was highly efficient in term of yields and selectivity. The authors suggested a rigid transition state in which the catalyst activates both the enol form of oxindole and the nitroalkene shielding the *Re* face of the donor.

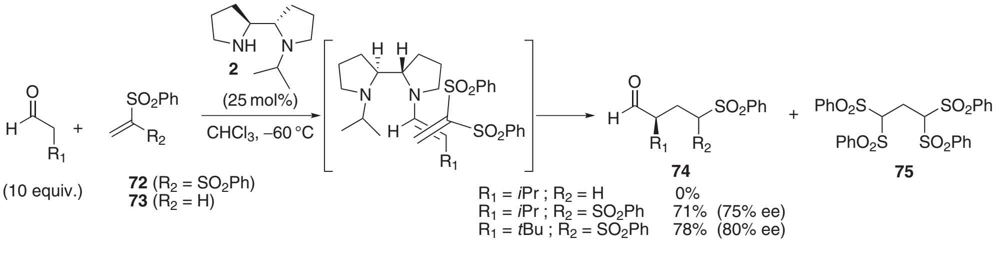


Scheme 34.25 Asymmetric addition of oxindoles to nitroolefins.

34.3
Addition to Vinyl Sulfones

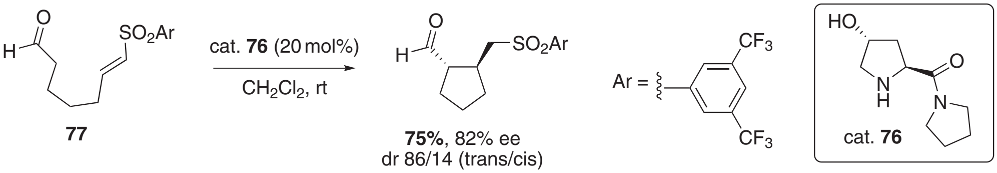
34.3.1
Enamine Activation of Aldehydes and Ketones

Mossé and Alexakis [66] reported in 2005 the first organocatalyzed 1,4-conjugate addition of aldehydes to vinyl sulfones. The organocatalyst, *N*-*i*Pr-2,2′-bipyrrolidine (**2**), induced a good enantioselectivity when using 1,1-bis(benzenesulfonyl) ethylene (**72**) while phenyl vinyl sulfone (**73**) was not reactive under the same conditions (Scheme 34.26). As product **74** is sensitive to silica gel, it is accompanied by byproduct **75.** To explain the observed selectivity, the authors suggested a transition state where the pyrrolidine moiety bearing the isopropyl substituent shields the *Re* face of the enamine and locks the conformation of the enamine intermediate.



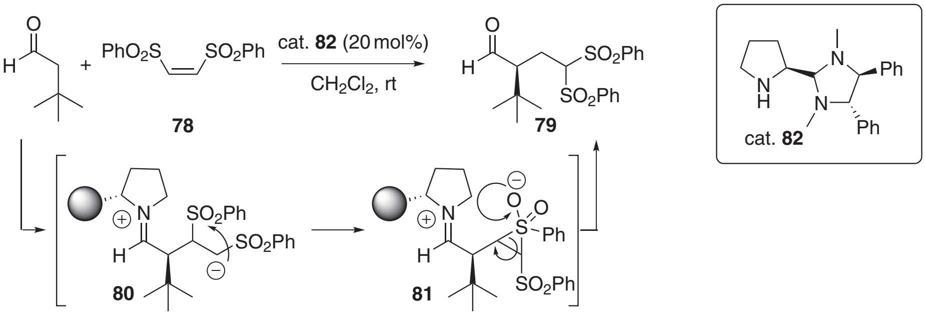
Scheme 34.26 Organocatalyzed conjugate addition to 1,1-bis(benzenesulfonyl)ethylene (**72**).

The intermolecular addition on the phenyl vinyl sulfone **73** was not described but it was demonstrated that an intramolecular version of this reaction was possible [67]. Amido-pyrrolidine **76** could promote the enantioselective cyclization of precursor **77** with a moderate level of selectivity (Scheme 34.27).



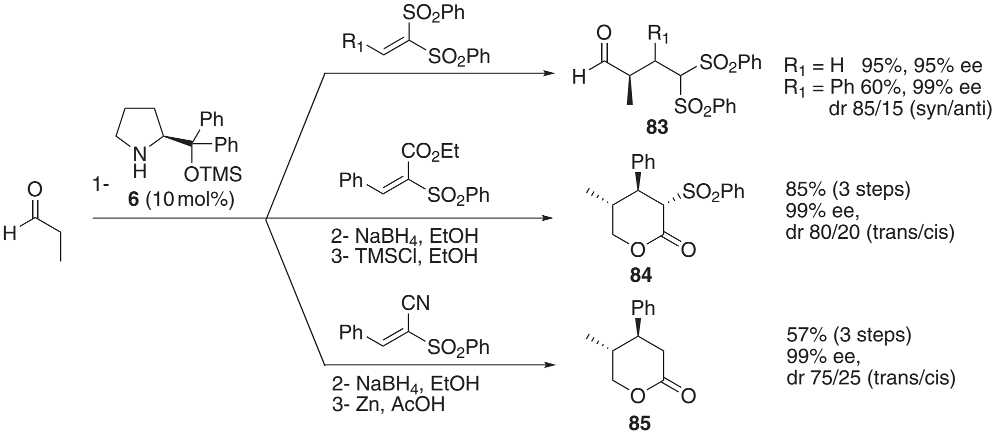
Scheme 34.27 Intramolecular addition on vinyl sulfones.

Quintard and Alexakis discovered an unprecedented rearrangement during the examination of new partners of 1,4-conjugate addition to vinyl sulfones [68]. The use of (*Z*)-1,2-bis(sulfone)vinylene (**78**) led to the same product (**79**) obtained when 1,1-bis(benzenesulfonyl)ethylene (**72**) was employed (Scheme 34.28), while (*E*)-1,2-bis(sulfone)vinylene led to deactivation of the catalyst. A plausible explanation for this rearrangement could be that attack of the anion **80**, resulting from the 1,4-addition on the adjacent sulfone, furnishes the cyclic species **81**, which would rearrange by ring opening.



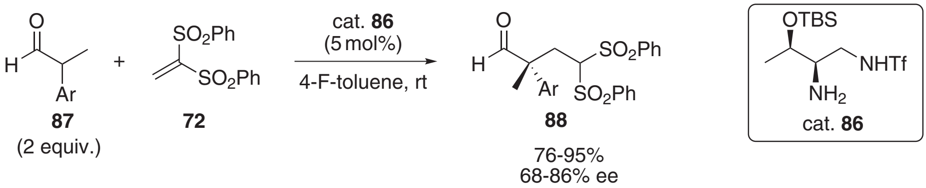
Scheme 34.28 Rearrangement of (*Z*)-1,2-bis(sulfone)vinylene (**78**) during organocatalyzed Michael addition.

A high level of enantioselectivity was reached with the use of diarylprolinol silyl ether but with good to moderate diastereocontrol. The groups of Lu [69] and Palomo [70] explored independently, with this class of catalyst, the addition of aldehydes to various vinyl sulfones, including acceptors bearing an ester or cyano group in the α position. Postfunctionalizations of the adducts afforded valuable building blocks such as lactones **84** and **85** (Scheme 34.29).



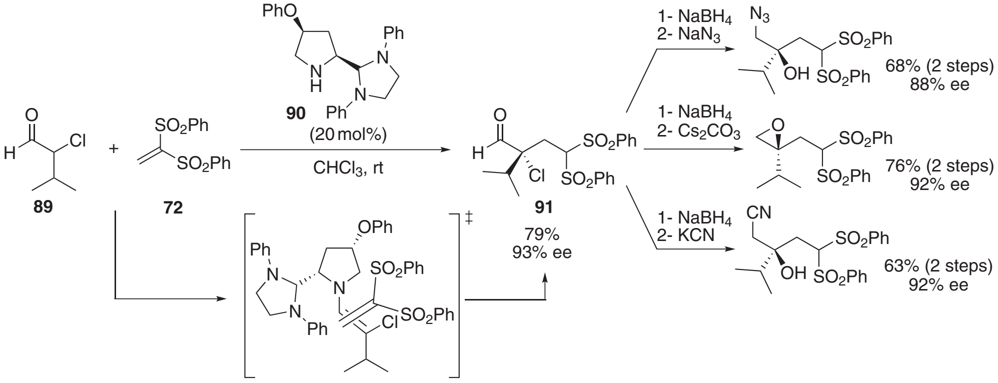
Scheme 34.29 Addition of propanal to vinyl sulfones and postfunctionalizations.

Primary amines were recently employed as organocatalysts in enamine activation of aldehydes and ketones in the conjugate addition of vinyl sulfones. Zhu and Lu screened several threonine derivatives bearing a sulfonamide moiety and found an interesting catalytic activity with compound **86** [71]. The authors used it to promote the addition of 2-arylpropanal (**87**) to 1,1-bis(benzenesulfonyl)ethylene (**72**), generating product **88** containing an all-carbon quaternary center (Scheme 34.30). The presence of the aryl group in donor **87** favors the imine–enamine tautomerization. Moderate to good enantioselectivity was observed during this transformation conducted at room temperature in an unusual solvent, 4-fluorotoluene.



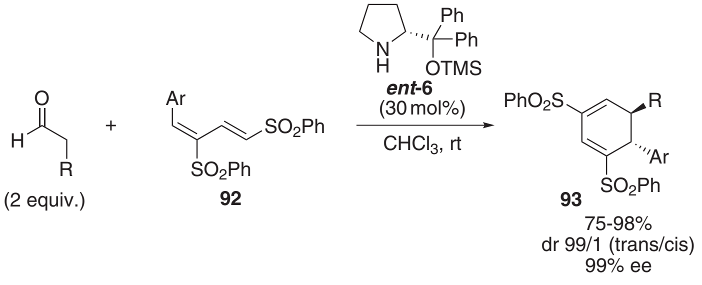
Scheme 34.30 Addition of α,α-disubstituted aldehydes to 1,1-bis(benzenesulfonyl)ethylene (**72**).

The addition of α-hetero-substituted aldehydes to disulfones **72** was examined by Quintard and Alexakis [72]. The presence of a heteroatom in the α-position of the aldehyde function increases the acidity of the hydrogen in the enolizable position and thus enhances the reactivity of the donor. α-Chloroaldehyde **89** gave excellent results in terms of yield and enantioselectivity using aminal catalyst **90** and offered a wide diversity of postfunctionalizations of adduct **91** that take advantage of the presence of the chlorine atom (Scheme 34.31). The high selectivity was explained by the authors through a transition state in which the enamine geometry is (*Z*) and the aminal and ether groups have a shielding effect on the *Re* face. This type of addition was also extended to α-oxygenated and α-nitrogenated aldehydes with high levels of enantioselectivity. The same group recently highlighted the importance of the nature of the group at C4 of the pyrrolidine ring on the global catalyst conformation [73].



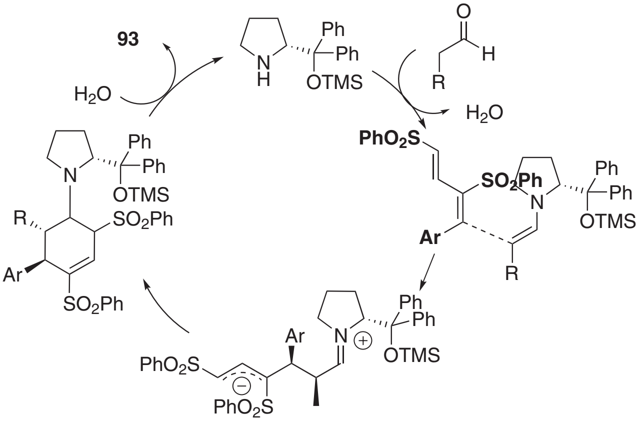
Scheme 34.31 Addition of α-chloroaldehydes to 1,1-bis(benzenesulfonyl)ethylene (**72**).

The groups of Alexakis and Stephens studied conjointly the 1,6-conjugate addition of aldehyde to dienic disulfone catalyzed by diphenylprolinol trimethylsilyl ether (*ent*-**6**) [74]. 1,3-Bis(sulfonyl)butadiene substrates **92** turned out to be exceptional acceptors to form chiral conjugated cyclohexadienes **93** with an impressive level of enantioselectivity, diastereoselectivity, and regioselectivity (Scheme 34.32). A high catalyst loading (30 mol%) was required for kinetic reasons. Indeed decreasing the loading to 10 mol% conserved the selectivity but increased the reaction time from 24 to 120 h.



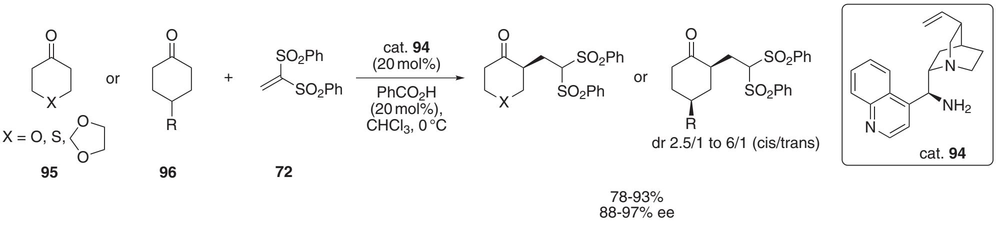
Scheme 34.32 Organocatalyzed conjugate addition to 1,3-bis(sulfonyl)butadiene **92**.

To explain the formation of **93**, the authors proposed a mechanism in which the 1,6-conjugate addition occurred through a synclinal transition state (Scheme 34.33). The bulky group on the pyrrolidine ring of the enamine intermediate acts as a shield for its *Re* face through steric repulsion. The resulting adduct seems to spontaneously cyclize before regeneration of the catalytic entity.



Scheme 34.33 Proposed catalytic cycle for the formation of cyclohexadiene **93**.

Quintard and Alexakis examined the catalysis of the addition of cyclic ketones to (*Z*)-1,2-bis(sulfone)vinylene **78** with their aminal secondary amine catalysts and obtained moderate enantioselectivities (64–73% ee) [75] while Lu's group used the more reactive and less sterically sensitive primary amines. The latter group [76] had shown that the primary amine derived from cinchonidine (**94**) was very efficient in this reaction with six-membered cyclic ketones **95** or prochiral ketones **96** (Scheme 34.34). Unprecedented enantioselectivity was obtained with this catalytic system on combining catalyst **94** and benzoic acid as additive under mild conditions while in the case of prochiral ketones **95** moderate diastereoselectivity was observed.

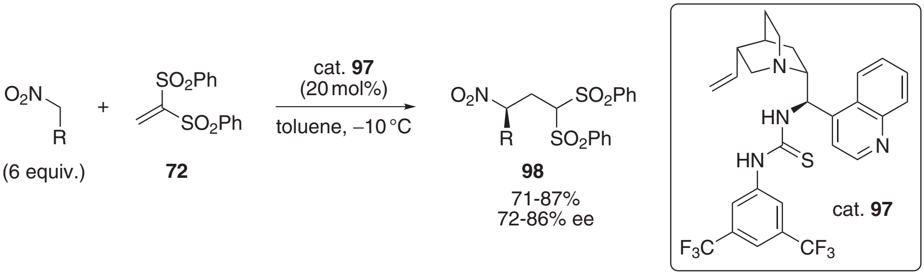


Scheme 34.34 Addition of ketones to 1,1-bis(benzenesulfonyl)ethylene (**72**).

While enamine activation of the donor was the most studied mode of activation, more recently non-covalent interactions between the catalyst and the substrates have been examined.

34.3.2
Non-Covalent Activation

Zhu and Lu reported the addition of nitroalkane to 1,1-bis(benzenesulfonyl)ethylene (**72**) [77] using Soos' organocatalyst [78], that is, the thiourea derived cinchona alkaloid **97** (Scheme 34.35). In the mechanism proposed by the authors, the tertiary amine moiety deprotonates the nitroalkane while the thiourea group activates the donor, with a H-bonding adding rigidity to the probable transition state. Adducts **98** were obtained with moderate to good enantioselectivities and were used for the synthesis of chiral amines.

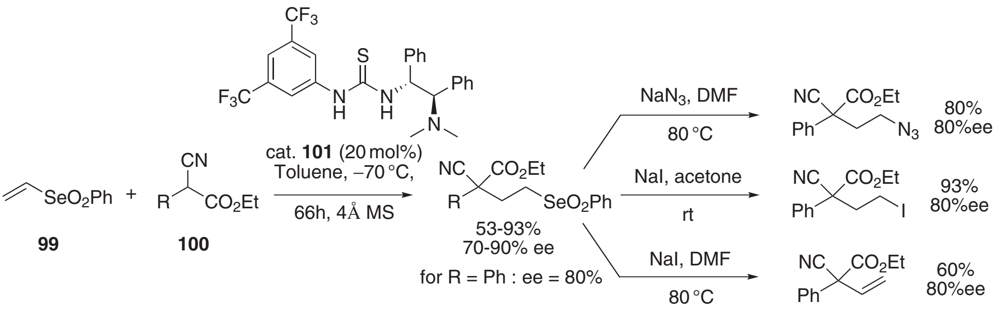


Scheme 34.35 Addition of nitroalkanes to 1,1-bis(benzenesulfonyl)ethylene (**72**).

At the same time as the emergence of the vinyl sulfones as Michael acceptors in organocatalyzed conjugate additions, a new type of acceptor appeared in the form of vinyl selenones.

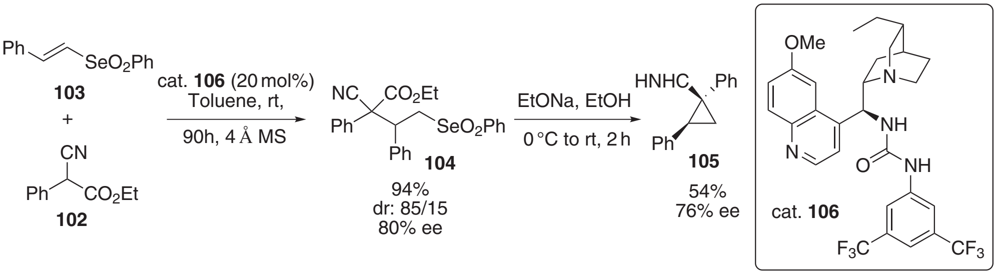
34.4
Addition to Vinyl Selenones

Vinyl selenones have appeared recently in organocatalysis as Michael acceptors and the corresponding adducts offered all the wealth of selenium chemistry. In 2009, the group of Marini inaugurated the first use of vinyl selenones as Michael acceptors in an organocatalyzed process using hydrogen bonding activation [79]. Selenone **99** was first examined with α-substituted cyanoacetate **100** using bifunctional catalyst **101**, which contains a tertiary amine and a thiourea (Scheme 34.36). When R is an aryl group, higher stereoselectivity was observed (76% < ee < 90%) than with an alkyl group. Moreover, several postfunctionalizations of the adduct were possible without alteration of the enantiomeric excess.



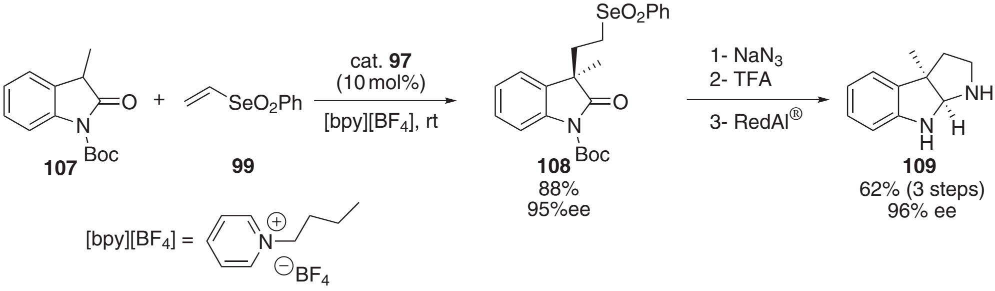
Scheme 34.36 Addition of α-cyanoesters to vinyl selenone **99** and postfunctionalizations.

The same group examined later a one-pot sequence involving the organocatalyzed conjugate addition of cyanoester **102** to β-substituted vinyl selenone **103** followed by a rearrangement leading to optically active cyclopropane **105** bearing a quaternary center [80]. They had to re-optimize this reaction and showed that urea **106**, derived from cinchona alkaloid, was the best catalyst for such a substrate. Noticeably, moderate diastereoselectivity and low enantioselectivity were observed in this case (Scheme 34.37) in comparison with those obtained when the acceptor was not β-substituted. The rearrangement of adduct **104**, promoted by addition of EtONa in ethanol, starts with a decarboxylation generating an enolate that cyclizes by displacement of the selenone. Through this process, which could be performed in a single pot with a change of the solvent, cyclopropane **105** was obtained with complete diastereoselectivity and only a slight erosion of enantioselectivity.



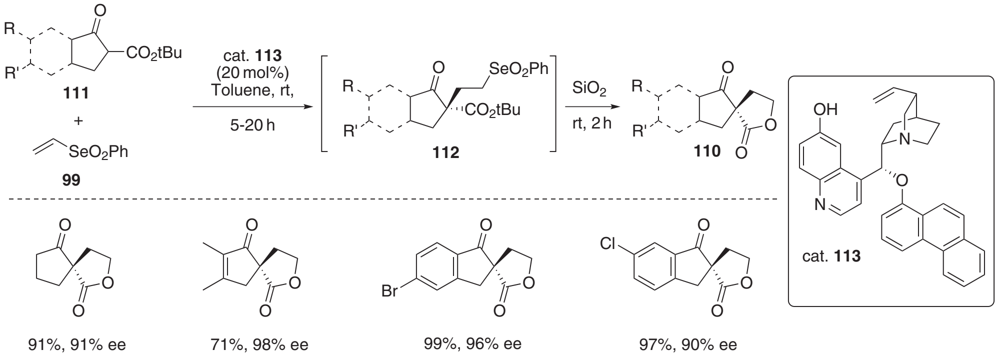
Scheme 34.37 Synthesis of cyclopropanes by sequential addition to vinyl selenone and cyclization.

Liu and Chen's group explored the use of oxindoles **107** as nucleophiles in conjugate addition to vinyl selenone **99** in the presence of Soos' thiourea **97** in an ionic liquid (Scheme 34.38) [81]. A high level of enantioselectivity was reached, suggesting, according to the authors, a highly organized transition state in which the thiourea moiety guides the vinyl selenone by H-bonding with the oxygen atoms on the selenone group. Adduct **108** was converted in three more steps – substitution of the selenone by sodium azide, deprotection of the Boc group, and reductive treatment by RedAl® – into aminal **109**, which constitutes the skeleton of several natural alkaloids.



Scheme 34.38 Synthesis of aminal **109**.

A highly efficient synthesis of spirolactone **110** was described by Marini *et al.* in 2011 [82] using the addition of cyclic β-ketoester **111** to vinyl selenone **99** and subsequent cyclization of intermediate **112** in the presence of silica (Scheme 34.39) under mild conditions. This reaction exhibited a wide scope (selected examples are given in Scheme 34.39) but was limited to β-ketoesters with a cyclopentanone core. Moreover this process could be extended to stereodivergent parallel kinetic resolution of a racemic mixture of chiral β-ketoesters with a high degree of enantioselectivity.



Scheme 34.39 Organocatalyzed spirolactonization.

The authors suggested a transition state (Figure 34.3) to explain the observed stereoselectivity in which the tertiary amine included in the catalyst **113** would be responsible for formation of the enolate, while the hydroxyl group would play a role in guiding the vinyl selenone by H-bonding.

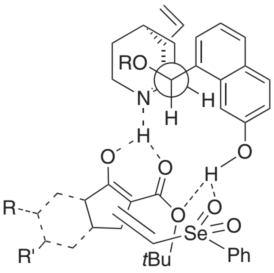


Figure 34.3 Transition state proposed to explain the selectivity observed.

34.5
Summary and Conclusions

Enantioselective conjugate addition to nitroolefins has, during the last five years, been a fruitful area of research in organocatalysis judging by the abundant number of published studies. After a beginning dominated mainly by covalent activation through an enamine intermediate, H-bonding activation has emerged more recently, offering the opportunity to use new types of nucleophiles and thereby expanding considerably the scope of this reaction. Addition to nitroolefins, despite the fact it is probably one of the most studied organocatalyzed reactions, remains an active field at the frontier of new research.

For the same sequence, vinyl sulfones and vinyl selenones have appeared as new partners in organocatalyzed asymmetric conjugate addition, giving access to valuable building blocks.

Acknowledgments

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35
Organocatalyzed Asymmetric Arylation and Heteroarylation Reactions

Renata Marcia de Figueiredo and Jean-Marc Campagne

35.1
Introduction

To achieve highly selective chemical transformations in which complex molecular structures can be obtained in a straightforward way remains a field of paramount importance in academia and industry. Among the main transformations allowing C–C and C–N bond formation, substantial emphasis should be placed on the Friedel–Crafts (F-C) reaction. Indeed, since its discovery in 1877 [1], this ubiquitous reaction has paved the way to very important classes of building blocks by allowing the functionalization of aromatic systems. Over the years, the very harsh initial conditions (stoichiometric amounts of Lewis acid, excessive heating) have been replaced by milder and more environmentally friendly methods. While the first reports on asymmetric F-C alkylations were described via metal-catalysis in the mid-1980s [2], nowadays the field of organocatalysis has been recognized as an efficient and complementary strategy for carrying out aromatic substitutions with very high levels of selectivity. This chapter does not give an exhaustive account but rather emphasizes the main progress in this rapidly expanding field [3]. To give a general overview, Figures 35.1–35.4 illustrate selected organocatalysts and representative nucleophiles and electrophiles used in asymmetric organocatalyzed F-C alkylation:

Organocatalysts: To date, the main classes of organocatalysts that have been used are [42]: imidazolidinone, diarylprolinol silyl ether, cinchona alkaloid, and phosphoric acid and thiourea derivatives. Essentially, two modes of activation can be considered: the reversible formation of iminiums/enamines (covalent activation) with α,β-unsaturated aldehydes and ketones in the presence of primary or secondary chiral amines (Figure 35.1), and activation via hydrogen-bond formation (non-covalent activation) when chiral catalysts bearing hydrogen-bond donors are used (Figure 35.2).

Aromatic nucleophiles: In the first reports on organocatalyzed asymmetric F-C reactions, indole and pyrrole derivatives were mainly used. Indeed, apart their aptitude in undergoing electrophilic substitutions, the indole derivatives

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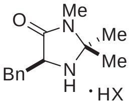

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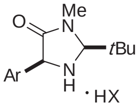

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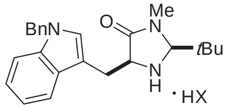
b Ar=1-naphthyl Ref. [5b]



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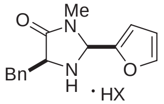

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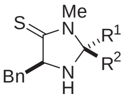

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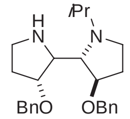

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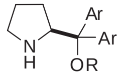
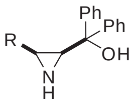
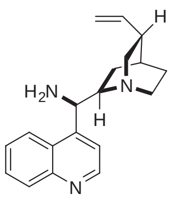


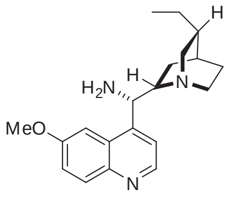
7
a R=TMS, Ar=Ph Ref.[10]
b R=TMS, Ar=3,5-$(CF_3)_2$Ph Ref.[11]
c R=TBDMS, Ar=Ph Ref.[12]
d R=TMS, Ar=$PhCH_2NMe_2$ Ref.[13]



8
Ref.[14]

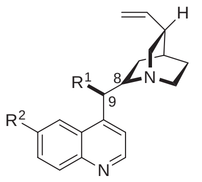


9
Ref.[15]



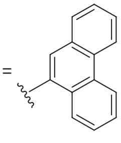
10
Ref.[16]

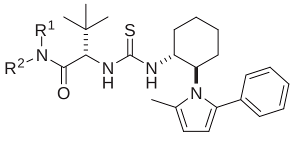
Figure 35.1 Representative primary and secondary chiral amines (iminium–enamine activation).



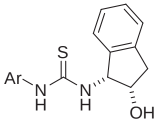
R^1	R^2	C8	C9	Catalyst
OH	H	*S*	*R*	**11** Ref.[17]
OH	H	*R*	*S*	**12** Ref.[17]
OPHN	OH	*S*	*R*	**13** Ref.[18]
OPHN	OH	*R*	*S*	**14** Ref.[18]
OBn	OH	*S*	*R*	**15** Ref.[19]
OH	OH	*S*	*R*	**16** Ref.[20]

PHN =

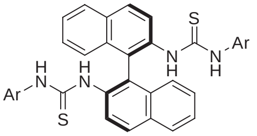




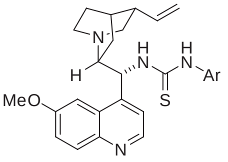
17 R^1=R^2=*i*Bu Ref.[21]
18 R^1=Me, R^2=*n*C_5H_{11} Ref.[22]



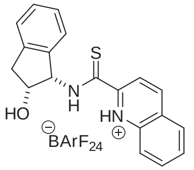
19 Ref.[23]
Ar = 3,5-$(CF_3)_2C_6H_3$



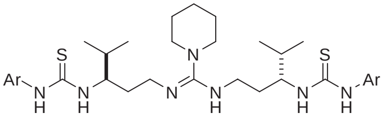
20 Ref.[24]
Ar = 3,5-$(CF_3)_2C_6H_3$



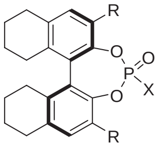
21 Ref.[25]
Ar = 3,5-$(CF_3)_2C_6H_3$



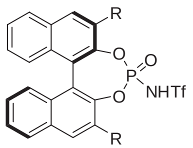
22 Ref.[26]



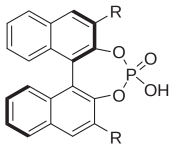
23 Ref.[27]
Ar = 3,5-$(CF_3)_2C_6H_3$



24
a R=$SiPh_3$, X=NHTf Ref.[28]
b R=$SiPh_3$, X=OH Ref.[29]
c R=$CHPh_2$, X=OH Ref.[30]
d R=1-naphthyl, X=OH Ref.[31]
e R=2-naphthyl, X=OH Ref.[32]



25
a R=4-NO_2-C_6H_4 Ref.[33]
b R=2,4,6-(*i*Pr)$_3C_6H_2$ Ref.[34]



26
a R=3,5-$(Ph)_2C_6H_3$ Ref.[35]
b R=2,4,6-$(Me)_3C_6H_2$ Ref.[36]
c R=3,5-$(CF_3)_2C_6H_3$ Ref.[37]
d R=1-naphthyl Ref.[38 *ent*-**26d**]
e R=2,4,6-(*i*Pr)$_3C_6H_2$ Ref.[39]
f R=$SiPh_3$ Ref.[40 ent-**26f**]
g R=2,4-$(CF_3)_2C_6H_3$ Ref.[41]

Figure 35.2 Representative chiral cinchona alkaloid, thiourea, and phosphoric acid derivatives (hydrogen bond activation).

are well-known as being very important building blocks in pharmaceuticals, agrochemicals, and material science [43]. Over the years, and with the development of very effective organocatalytic systems, new classes of aromatic nucleophiles known for being less prone to aromatic substitutions were employed, such as, for example, aniline, naphthol, and benzene derivatives (Figure 35.3).

Electrophiles: The most used classes of electrophiles in asymmetric organocatalyzed F-C reactions are α,β-unsaturated aldehydes or ketones, nitroolefins, carbonyl compounds, and imines (see next section) (Figure 35.4).

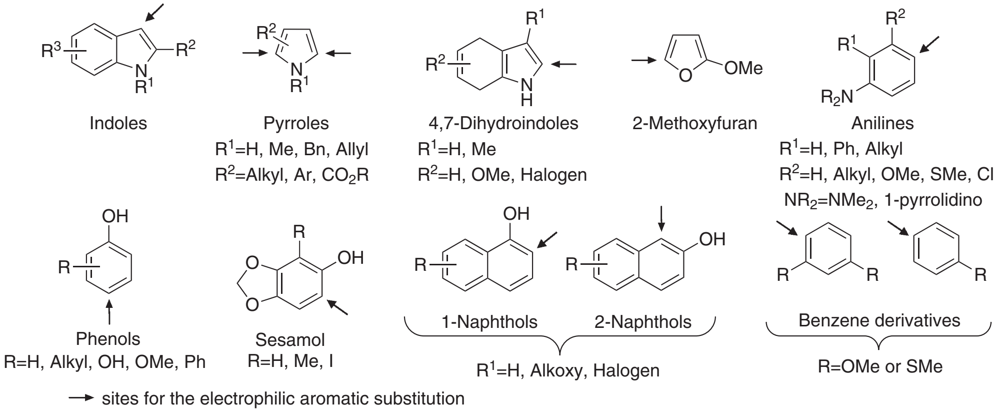


Figure 35.3 Representative aromatic nucleophiles.

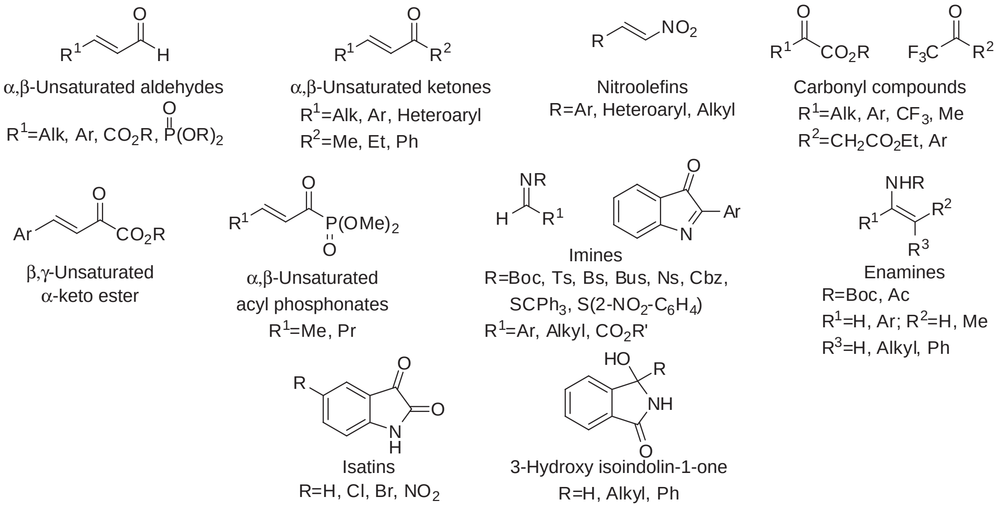


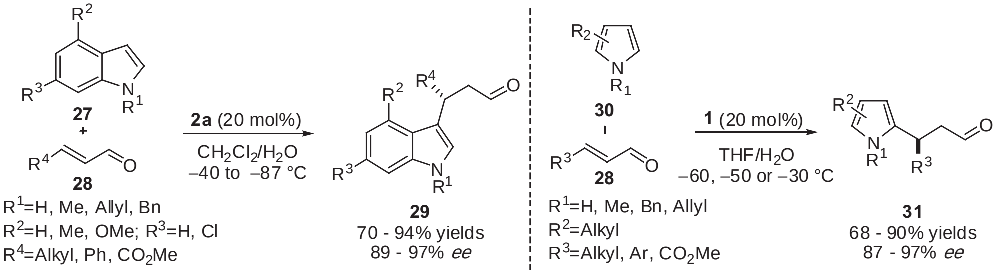
Figure 35.4 Representative electrophiles.

After this general overview, a brief survey of the key achievements in this area is given by highlighting some selected transformations according to the main classes of electrophiles. We will then summarize the asymmetric organocatalyzed F-C reaction in sequential processes (cascade, domino, tandem reactions) and, finally, illustrate its potential in some selected outstanding natural product syntheses.

35.2
Representative Classes of Electrophiles

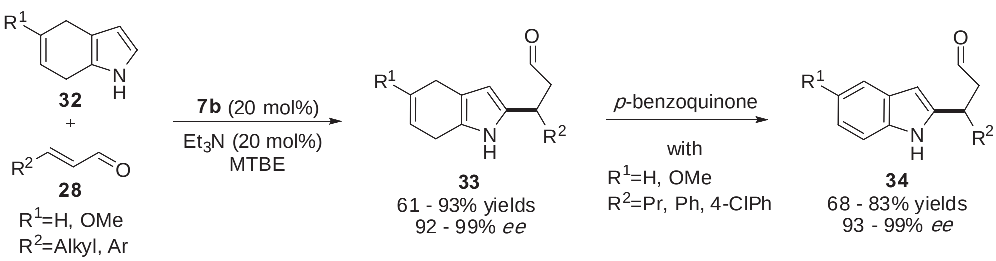
35.2.1
α,β-Unsaturated Aldehydes

In 2001, the reaction of pyrroles and indoles with α,β-unsaturated aldehydes in the presence of chiral imidazolidinones were the first reported examples of enantioselective organocatalyzed F-C alkylations (Scheme 35.1) [4, 5a].



Scheme 35.1 MacMillan's F-C alkylations with α,β-unsaturated aldehydes.

Since the publication of these works, the concept of LUMO-lowering activation of α,β-unsaturated aldehydes has been extended to a broad number of transformations. As examples we can cite the utilization of α-branched aldehydes [7], intramolecular reactions [44–46], and the use of anilines derivatives as nucleophilic aromatic systems [47, 48]. Diarylprolinol silyl ether analogs were also successfully used in such approaches. An example with 4,7-dihydroindoles, which after oxidation afford 2-substituted indole derivatives, is illustrated in Scheme 35.2 [11].

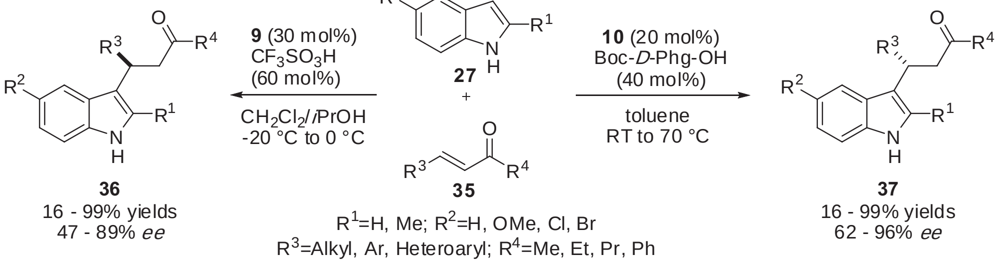


Scheme 35.2 F-C alkylations of 4,7-dihydroindoles with α,β-unsaturated aldehydes.

It might be pointed out that, in 2007, the concept of SOMO catalysis was employed for F-C alkylation with simple aldehydes. The reaction of octanal with *N*-Boc-pyrrole afforded the formyl α-arylated product in 85% yield and 84% ee [49]. Following this preliminary encouraging report, intramolecular F-C type α-arylations of simple aldehydes incorporating electron-rich aromatic nuclei were reported in 2009 with proposed mechanisms based on MacMillan's SOMO activation [5, 50b] (see Section 35.4, Scheme 35.29 for detailed examples).

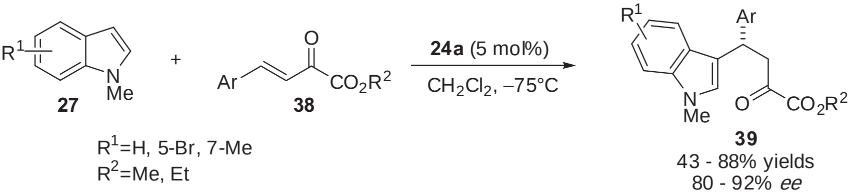
35.2.2
α,β-Unsaturated Enones

Although α,β-unsaturated aldehydes have been used extensively in F-C alkylations since 2001, the first report on α,β-unsaturated enones as electrophiles appeared only in 2006 [51]. In this publication, indole reacts with 5-methyl-3-hexen-2-one to afford the desired product in moderate yield (52%) and low enantioselectivity (28% ee). One year later, two independent groups showed that the utilization of primary amines **9** and **10** derived from natural cinchona alkaloids facilitates the iminium formation with unsaturated enones instead of hindered secondary amine catalysts [15, 16]. It should be emphasized that in both cases the use of an acidic co-catalyst is necessary to achieve the transformations. Nevertheless, only the second one, with catalyst **10**, profited from an asymmetric counterion-directed organocatalytic system (ACDC) [52] (Scheme 35.3).



Scheme 35.3 Chiral primary amines as organocatalysts with α,β-unsaturated enones.

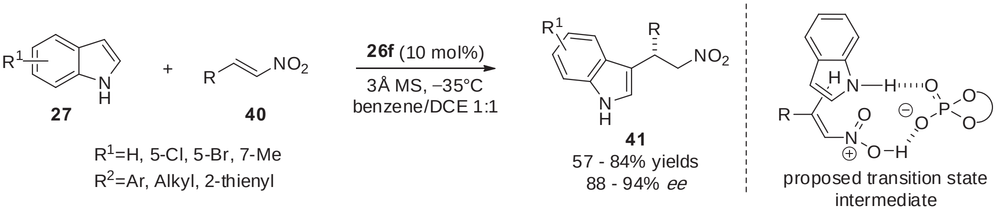
Chiral phosphoric acid analogs as catalysts in the F-C alkylation reaction of indoles with α,β-unsaturated aromatic enones were also devised [53]. β,γ-Unsaturated α-ketoesters were also used as electrophiles in organocatalyzed F-C alkylations of indoles and 2-naphthols. With indoles, chiral acidic *N*-triflylphosphoramide was successfully employed (Scheme 35.4) [28], whereas in the presence of 2-naphthols a thiourea-based catalyst showed better capacity to mediate a sequential F-C/cyclization process, giving naphthopyran scaffolds in moderate yields and selectivities (up to 90% ee) [54]. Recently, α,β-unsaturated acyl phosphonates were effectively used as hydrogen bond acceptors for F-C alkylations of indole derivatives in the presence of thiourea catalyst *ent*-**19** [55].



Scheme 35.4 Selected example of β,γ-unsaturated α-ketoesters as electrophile.

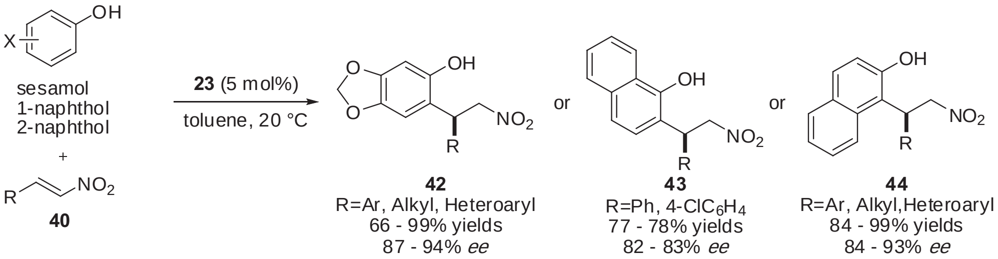
35.2.3
Nitroolefins

Nitroolefins are very attractive and effective Michael acceptors for F-C alkylations due to the strong electron-withdrawing nature of the nitro group, which, in addition, can easily be converted into other valuable functionalities. Chiral thioureas **19**, **20**, and **22** were used to prepare 2-indolyl-1-nitro-ethanes via the F-C alkylation of indole derivatives with nitroolefins [23, 24, 26]. 2-Naphthols as nucleophiles were also described with this class of electrophile, affording the F-C adduct in good yields and excellent enantioselectivities in the presence of a chiral thiourea [56]. Interestingly, extended reaction times (6 days versus 4 days) give rise, sluggishly, to unexpected N-disubstituted hydroxylamines instead of the Michael-type adduct that is obtained after 4 days. In 2008, nitroolefins were efficiently activated by phosphoric acids (Scheme 35.5) [57], and, recently, the conformationally flexible



Scheme 35.5 F-C alkylation between indoles and nitroolefins with phosphoric acid as catalyst.

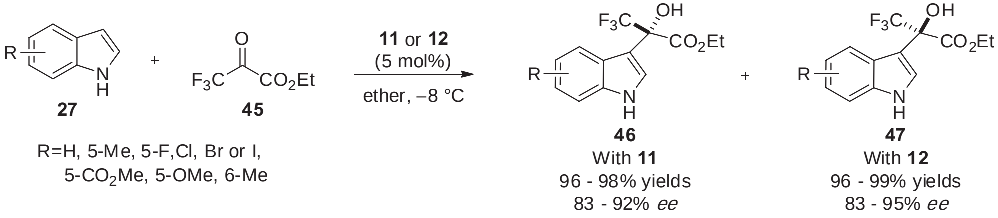
guanidine/bis-thiourea **23** was found to promote *ortho*-selective 1,4-type F-C alkylations of phenols with nitroolefins (Scheme 35.6) [27].



Scheme 35.6 F-C alkylation between sesamol, 1-naphthol, and 2-naphthol with nitroolefins.

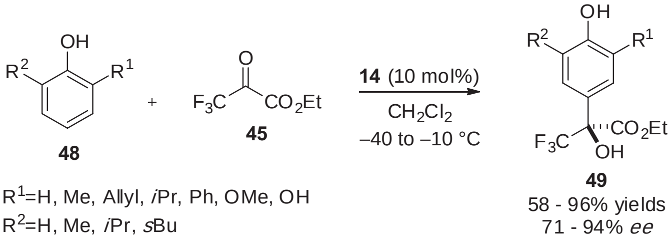
35.2.4
Carbonyl Compounds

Cinchona alkaloids were used in 2005 to catalyze the enantioselective hydroxyalkylation of indoles with ethyl trifluoropyruvate (**45**) as electrophile in excellent yields and selectivities (Scheme 35.7) [17].



Scheme 35.7 Cinchona alkaloid catalyzed hydroxyalkylation of indoles.

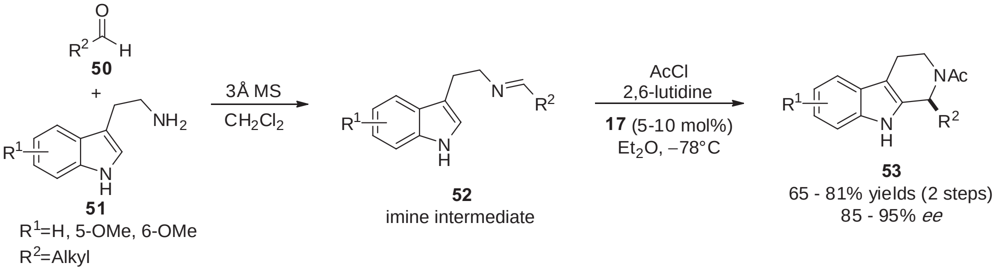
The scope of this F-C hydroxyalkylation of indoles was extended to a range of different carbonyl compounds, giving rise to the desired compounds in high yields (up to 97%) and enantioselectivities (up to 99% ee) in the presence of catalysts **13** and **14** [18]. Catalyst **14** also proved to be highly selective when carrying out the first example of cinchona alkaloid mediated F-C alkylation of phenols with **45** (Scheme 35.8) [58]. Chiral phosphoric acids were also used to mediate F-C alkylation in the presence of ethyl trifluoropyruvate [31], trifluoroacetate [59], and trifluoromethyl ketones [60].



Scheme 35.8 Cinchona alkaloid catalyzed hydroxyalkylation of phenols.

35.2.5
Imines (Aza-Friedel–Crafts Reaction)

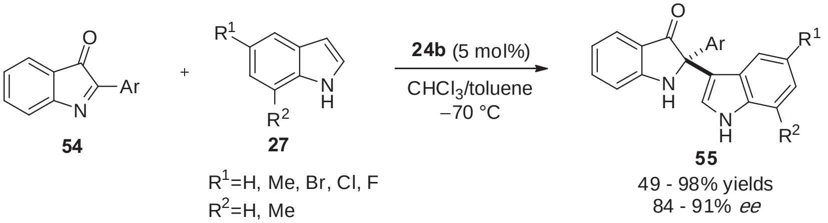
Since 2004, imines have represented another important class of electrophiles that has been extensively used in aza-F-C alkylation. The first example reported in the literature is illustrated in Scheme 35.9, showing an enantioselective acyl-Pictet–Spengler reaction via condensation of tryptamine with aliphatic aldehydes in the presence of **17** and acetyl chloride to afford substituted tetrahydro-β-carbolines [21]. In this process, activation of the intermediate imine **52**, as *N*-acyliminium species, is crucial for the reaction outcome: no reaction occurs in the absence of AcCl.



Scheme 35.9 Pictet–Spengler reaction via condensation of tryptamine with aldehydes.

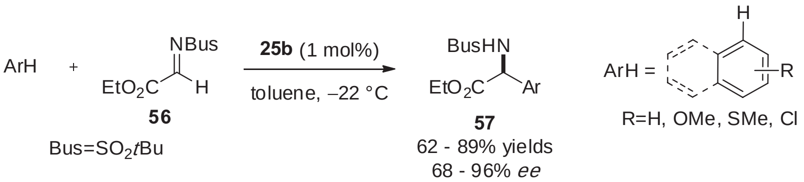
Two years later, thiourea **21**, functionalized with a cinchona alkaloid, was efficiently used in the synthesis of 3-indolylmethanamines in good yields and selectivities (up to 96% ee) [25]. The transformation takes place in the presence of aromatic, aliphatic, and heteroaromatic imine analogs. Chiral phosphoric acids **26a**, *ent*-**26d**, and *ent*-**26f** were also identified as efficient catalysts for the F-C alkylation between indoles and imines [35, 38, 40]. In these cases, in contrast with thiourea **21**, the processes were only successful in the presence of aromatic imines. More recently, the fruitful use of a thiourea supported on mesoporous silica (heterogeneous bifunctional catalyst) was reported [61]. The catalyst can be easily separated from the reaction mixture by simple filtration and reused several times without erasing the enantioselectivity.

In 2011, the first reports appeared on cinchona alkaloid mediated aza-F-C type reactions in the presence of 1-naphthol [62] and 2-naphthol [63] derivatives as nucleophiles. Although acyclic imines were extensively used as electrophiles, cyclic imines were only employed for the first time in 2011 for the synthesis of optically active indolindolinone derivatives **55** in high yields and selectivities [29] (Scheme 35.10).



Scheme 35.10 Aza-Friedel–Crafts reaction with cyclic imines.

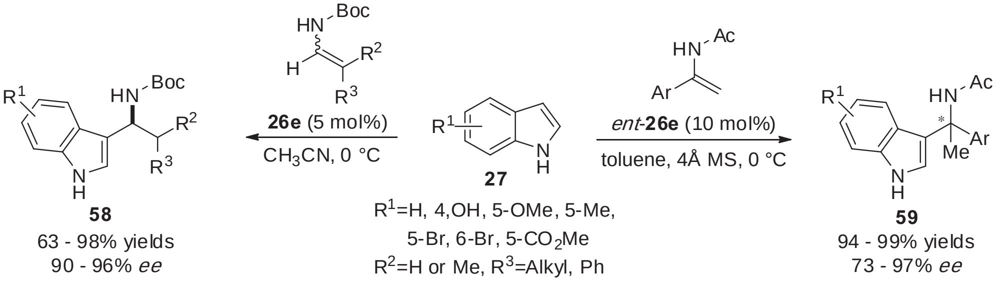
N-Boc-protected ethyl trifluoropyruvate imine was effectively used in a F-C reaction with indole derivatives for synthesizing, in high selectivities, quaternary α-amino acids via catalysis with chiral phosphoric acid **26e** [64]. A binaphthyl-based chiral sulfonimide [42c] and a chiral squaramide-based hydrogen bond donor [42a] were used as effective catalysts for promoting F-C reaction of indoles with imines. Recently, the F-C alkylation of arenes with glyoxylate imine was described via a chiral phosphoric acid (Scheme 35.11) [34].



Scheme 35.11 F-C alkylation of arenes with glyoxylate imine.

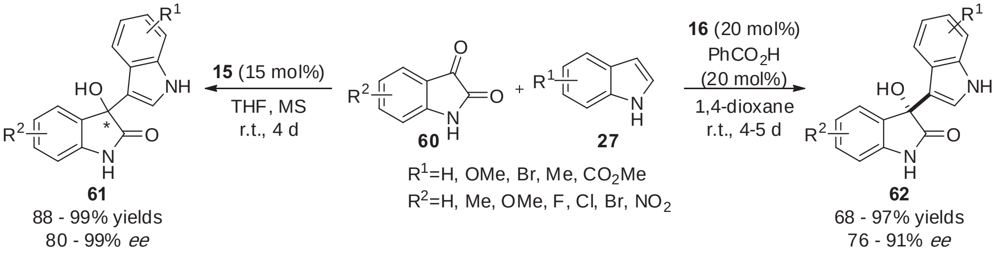
35.2.6
Other Electrophiles

Whereas α,β-unsaturated aldehydes and enones, nitroolefins, and imines have been used extensively in organocatalyzed enantioselective F-C reactions with various aromatic nucleophiles since 2001, the introduction of new classes of electrophiles in such transformations only started in the last four or five years. In 2007, two independent groups described how *N*-protected enamines could act as good substrates for preparing, in the presence of chiral phosphoric acids **26e** and *ent*-**26e**, new enantiomerically enriched indolylmethanamines (Scheme 35.12) [65]. More recently, *N*-acyl-iminium ions were successfully employed in an intermolecular thiourea-mediated addition of indoles, affording the desired products in moderate-to-good yields and high selectivities (up to 99% ee) [66].



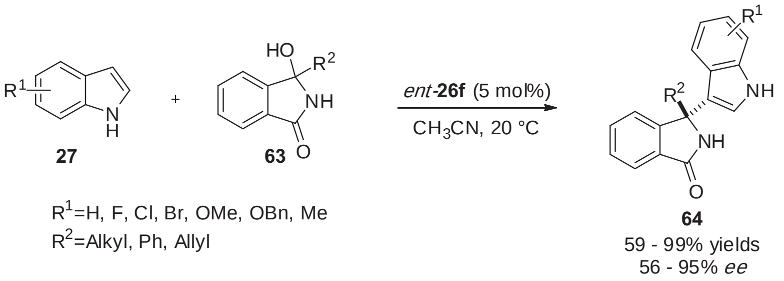
Scheme 35.12 Enamines in enantioselective organocatalyzed F-C alkylations.

Three years later, two groups independently described the asymmetric addition of indoles to isatins to give, in a straightforward manner, 3-indolyl-3-hydroxy-2-oxindole derivatives **61** and **62** (Scheme 35.13) [19, 20]. In these examples, quaternary stereogenic centers are created in high yields and excellent enantioselectivities (up to 99% ee).



Scheme 35.13 F-C alkylation with isatins: creation of quaternary stereogenic centers.

Chiral phosphoric acids **24e** and *ent*-**26f** have been used recently to promote enantioselective F-C alkylations of indoles with 3-substituted 3-hydroxyisoindolin-1-ones **64** (Scheme 35.14) [32, 67]. Moreover, α,α-dicyanoolefins have also been used in association with 2-naphthols for the synthesis of naphthopyrans in high yields (up to 99%) and good selectivities (up to 90% ee) via hydrogen-bonding thiourea catalysis [68].

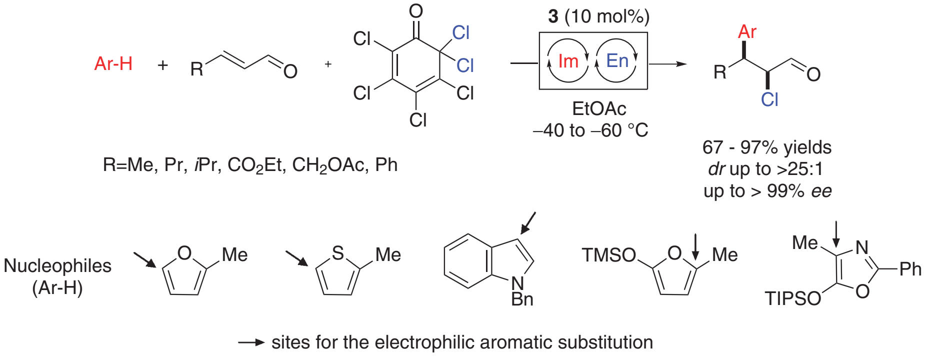


Scheme 35.14 3-Substituted 3-hydroxyisoindolin-1-ones as electrophiles.

35.3
Friedel–Crafts in Organocascade Transformations

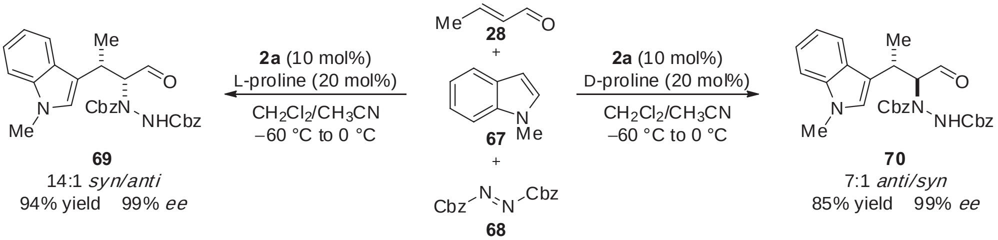
The increasing need for complexity and structural diversity is the driving force by which organic chemists have been developing highly selective, atom economic, and environmentally friendly organic transformations. For this purpose, special attention can be given to organocascade reactions [69]. One of the biggest advantages of such transformations is the possibility of promoting at least two transformations in a single reaction step under the same reaction conditions [70]. Furthermore, distinct modes of activation often enable organocatalysts to coexist in the same reaction medium without deleterious interactions. Even though very impressive accomplishments have been made in single event organocatalyzed enantioselective F-C reactions, as illustrated in the previous section, remarkable work in organocascade processes has also been developed. In fact, when combined with other transformations, the F-C reaction has rendered possible the construction of very complex molecular entities and, in some remarkable cases, allowed the synthesis of natural products (see next section for selected examples).

The first example of dual organocascade catalysis involving iminium/enamine activation was published in 2005 (Scheme 35.15) [6]. In this report, α,β-unsaturated



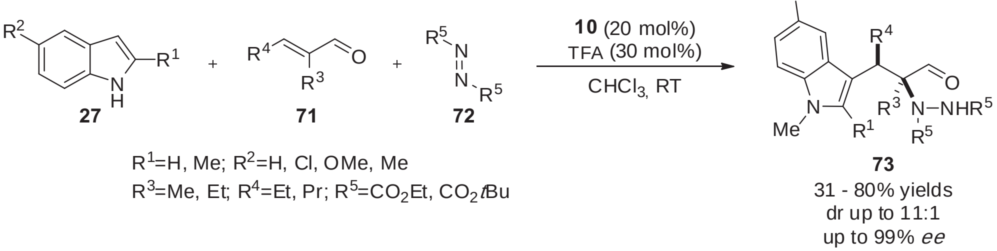
Scheme 35.15 First example of organocascade catalysis involving F-C alkylation.

aldehydes were exposed to imidazolidinone **3** to generate iminium species that could efficiently react with a range of nucleophiles via a F-C alkylation type reaction. The conjugate addition adduct then obtained enters in a second catalytic cycle, via enamine activation, enabling highly diastereoselective addition to electrophile **65**. In addition, these two orthogonal modes of activation of carbonyl compounds could also be mediated by two different secondary amines, thus affording the possibility of accessing, in a single operation, the two different diastereoisomers **69** and **70** in high yields and selectivities (Scheme 35.16) [71].



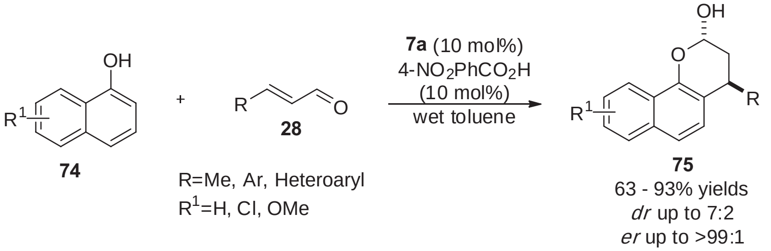
Scheme 35.16 Olefin arylamination: selectivity modulated by a combination of organocatalysts.

An innovative strategy for an organocascade reaction in the presence of *N*-methylindole, 2-hexenal, and methyl vinyl ketone was also developed via iminium and enamine catalysis [72]. In this remarkable work, incompatible catalytic systems were combined in a one-pot sequence for an elegant asymmetric multistep reaction via site isolation with soluble "star polymers." In addition, primary amines derived from cinchona alkaloids were successfully used as catalysts for the intermolecular organocascade aryl-amination of α-substituted α,β-unsaturated aldehydes **71** with indoles (Scheme 35.17) [73]. The use of primary amines instead of secondary amines rendered possible the α,β-difunctionalization of α-substituted α,β-unsaturated enals, a longstanding challenge in aminocatalysis. Indeed, in this special case a very sluggish enamine-activation rate, or even inert capacity, is generally observed with secondary amines, which usually give rise to a complete absence of enantiocontrol at the α-position of the aldehyde function.



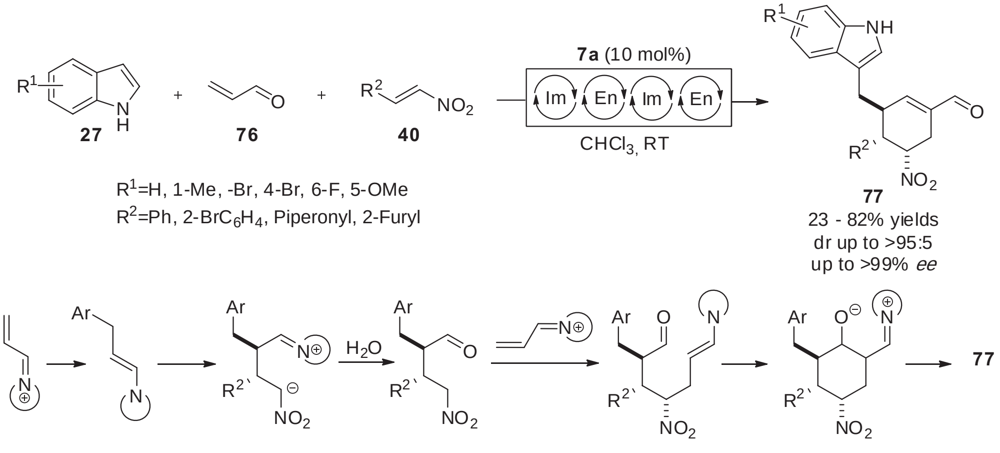
Scheme 35.17 α,β-Difunctionalization of α-substituted α,β-unsaturated enals via an organocascade.

Phosphoric acid **25a** was successfully employed for mediating enantioselective synthesis of 1,3-disubstituted isoindolines from electrophilic bifunctional substrates (containing an imine and a Michael acceptor site) and indoles [33]. Catalyst **7a** was used effectively in an organocatalytic asymmetric F-C alkylation/cyclization cascade reaction between 1-naphthols and α,β-unsaturated aldehydes to give chromanes in good yields and selectivities (Scheme 35.18) [10]. Furthermore, 2-naphthols and β,γ-unsaturated α-keto ester also reacted in a F-C alkylation/dehydration sequence, in the presence of a thiourea catalyst and a catalytic amount of concentrated sulfuric acid, affording optically active naphthopyran derivatives [54].



Scheme 35.18 Organocatalytic F-C alkylation/cyclization cascade reaction.

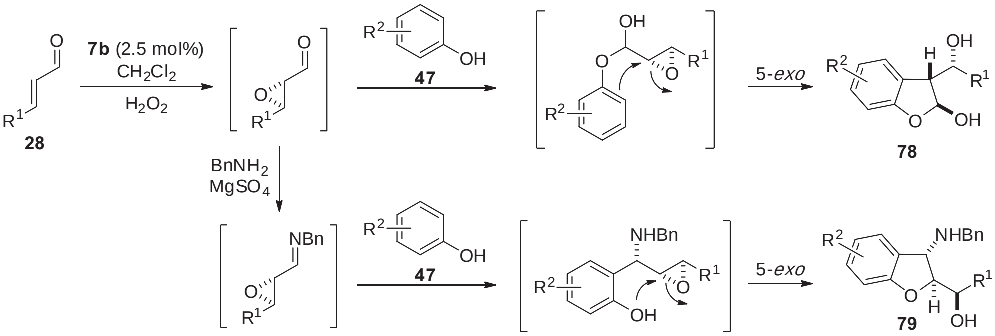
The use of phosphoric acid *ent*-**26d** for the catalysis of a tandem double F-C reaction gave rise to fluorene derivatives (up to 96% ee) by the reaction between indoles and 2-formylbiphenyl derivatives [74]. Vinyl indole derivatives combined with α,β-unsaturated aldehydes gave rise to functionalized tetrahydrocarbazoles with two or more stereocenters via an intermolecular triple cascade process by means of secondary amine **7a** catalysis [75]. Catalyst **7a** also promoted a quadruple F-C/Michael/Michael/aldol condensation reaction between indoles, acrolein, and aromatic nitroolefins (Scheme 35.19) [76]. This work provides a straightforward



Scheme 35.19 Organocatalytic quadruple cascade reaction.

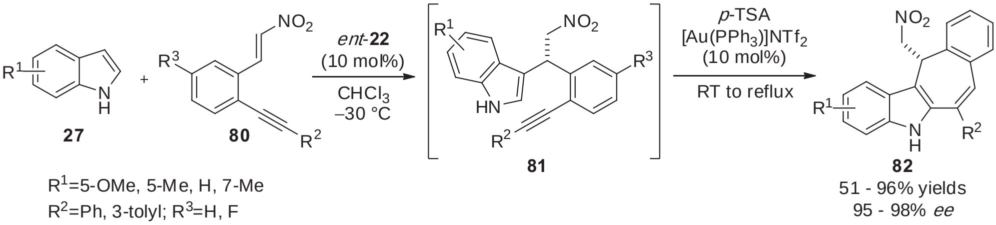
entry to 3-(cyclohexenylmethyl)indoles bearing three contiguous stereogenic centers. Recently, 5-hydroxyfuran-2(5*H*)-one and indoles have been used in a sequential F-C/Ugi four-center three-component reaction (U-4C-3CR), affording γ-lactams in high yields and selectivities [77]. This work demonstrates well that the use of a more functionalized electrophile paves the way to the possibility of increasing complexity and structural diversity after the initial F-C reaction.

An impressive example that illustrates the power of F-C type reactions in diversity-oriented one-pot reaction cascades was reported recently (Scheme 35.20) [78]. In this study, optically active *trans*-2,3-dihydrobenzofurans **78** and **79** having three stereogenic centers were prepared in a straightforward manner by simple modification of the structure of the key intermediates, which resulted in different chemoselectivity of the organocascade reactions.



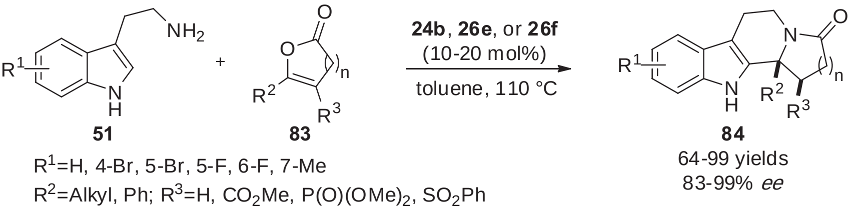
Scheme 35.20 Organocatalytic approach to 2,3-dihydrobenzofurans.

Notably, the emerging field of combining organo- and transition-metal-catalysis [79] was used recently to promote indole annulations affording tetracyclic seven-membered-ring-containing derivatives (Scheme 35.21) [80]. The dual thiourea *ent*-**22**/gold catalysis allowed the insertion of a stereogenic center into a highly conjugated tetracyclic system through two sequential electrophilic aromatic substitution reactions.



Scheme 35.21 Thiourea/gold catalysis in two sequential electrophilic aromatic substitutions.

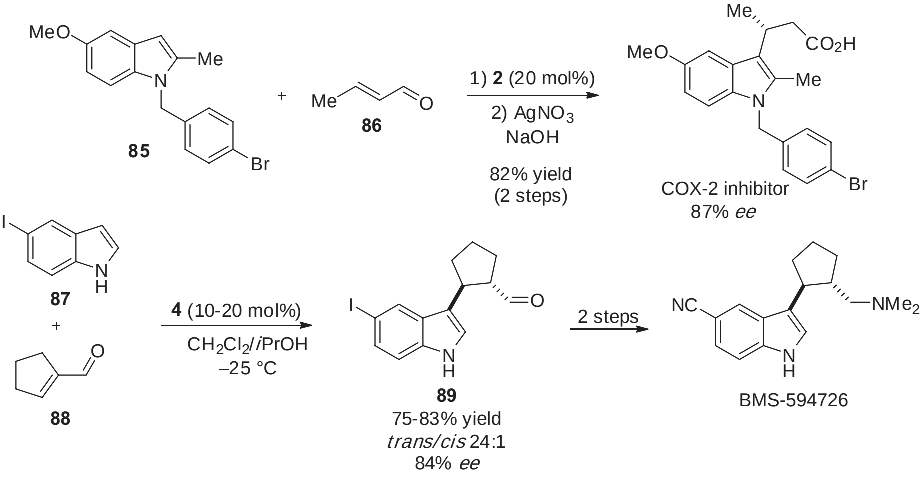
Scheme 35.22 gives an example of Brønsted acid-catalyzed *N*-acyliminium cyclizations. Here, chiral phosphoric acids **26e**, **26f**, or **24b** were used to carry out highly selective cascade Pictet–Spengler-type reaction of tryptamines **51** and enol lactones **83** [81].



Scheme 35.22 Chiral phosphoric acids in a cascade Pictet–Spengler-type reaction.

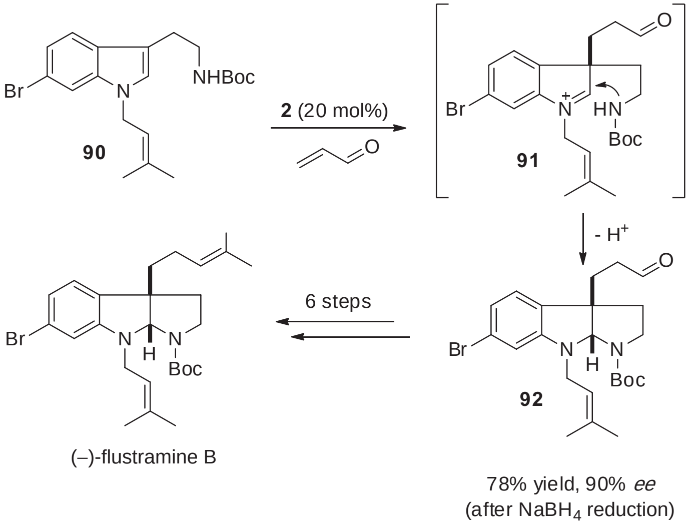
35.4
Application in Biologically Interesting and Natural Product Syntheses

Unsurprisingly, owing to the broad structural complexity and diversity that can be reached by means of organocatalyzed enantioselective F-C type reactions, this reaction has been used as a valuable tool in the field of total synthesis of natural products. Indeed, alone or in association with other transformations (cascade), the F-C reaction represents one of the most effective ways to construct C–C and C–N bonds between aromatic nucleophiles and various electrophiles. Within this context, the power of enantioselective alkylations of indoles with enals in the total synthesis of biologically attractive scaffolds was well illustrated during the preparation of a COX-2 inhibitor [5], and the synthesis of a selective serotonin reuptake inhibitor BMS-594726 by the group of King (Scheme 35.23) [7]. The latter work constitutes the first example in which an α-branched enal was used as electrophile in an organocatalyzed F-C alkylation.



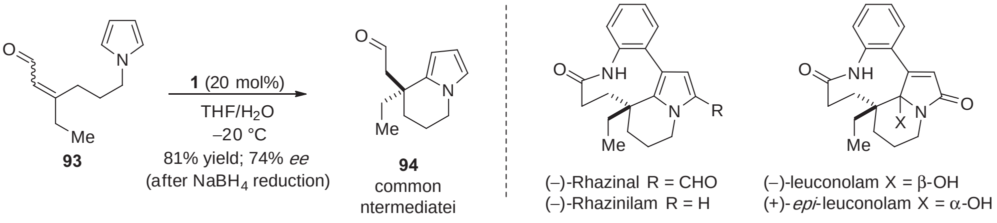
Scheme 35.23 Asymmetric alkylation of indoles with enals.

In an elegant synthesis of the marine alkaloid flustramine B, MacMillan and coworkers have used catalyst **2** to promote the first organocatalytic addition/cyclization process that allows the preparation of the chiral pyrroloindoline motif in a single step [82]. The transformation occurs between 6-bromotryptamine derivative **90** and acrolein via the intermediary formation of indolium ion **91**, which is in turn readily trapped in an intramolecular way by the Boc-amino group, giving rise to intermediate **92** (Scheme 35.24). Then, six further additional steps were necessary to accomplish the synthesis of (–)-flustramine B.



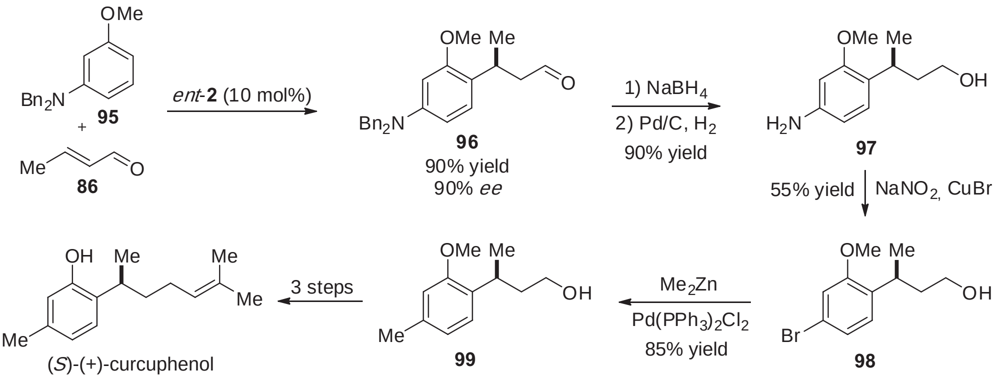
Scheme 35.24 Synthesis of (–)-flustramine B.

Recently, the group of Hanessian reported an extension of MacMillan's organocatalytic aromatic alkylation to 3-aminocrotonaldehyde in the concise synthesis of an advanced precursor of a drug prototype for the treatment of migraine headaches [83]. An example that does not involve indoles as aromatic nucleophiles but pyrroles in the synthesis of natural products was reported in 2006 by Banwell and coworkers [84]. They accomplished, via the common intermediate **94** obtained by means of an intramolecular F-C type alkylation, the syntheses of the alkaloids (–)-rhazinal, (–)-rhazinilam, (–)-leuconolam, and (+)-*epi*-leuconolam via the highly enantioselective creation of a quaternary stereocenter (Scheme 35.25).



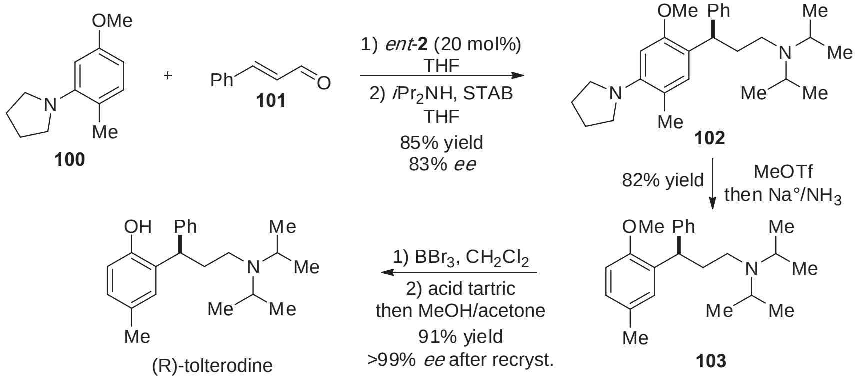
Scheme 35.25 Intramolecular F-C alkylation and creation of quaternary stereocenters.

The iminium strategy was elegantly extended to asymmetric alkylations of activated benzenes by the groups of Kim [85] and MacMillan [86]. Kim and coworkers have accomplished the total synthesis of (*S*)-(+)-curcuphenol, in which an organocatalytic alkylation of *N,N*-dibenzyl-3-anisidine (**95**) promoted by *ent*-**2** was among the key steps. Interestingly, the dibenzylamino group could be replaced by other functionalities, allowing, after three additional steps, the synthesis of (*S*)-(+)-curcuphenol, a bioactive sesquiterpene phenol with antifungal, antitumor, and antimalarial activity (Scheme 35.26).



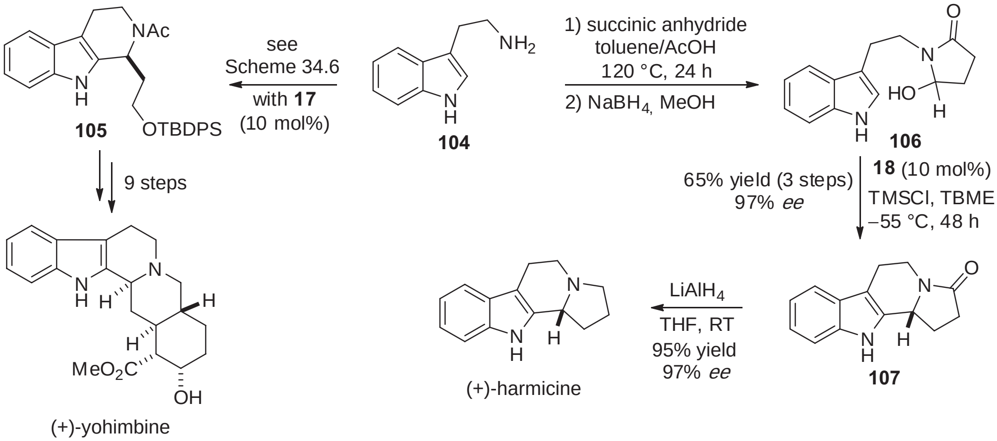
Scheme 35.26 Synthesis of (*S*)-(+)-curcuphenol.

In addition, an asymmetric synthesis of (*R*)-tolterodine, a potent muscarinic receptor antagonist used on a worldwide basis for the treatment of urge incontinence, was devised by MacMillan's group. Their own imidazolidinone-mediated electrophilic aromatic substitutions of anilines in concert with a new methodology for aryl ammonium reduction (MeOTf/Na^0/NH$_3$) gave rise to the above-mentioned pharmaceutical agent in a concise and efficient manner (Scheme 35.27).



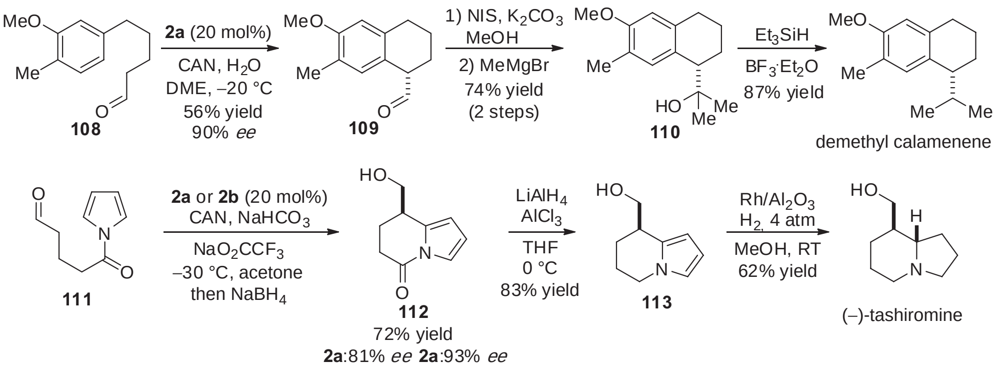
Scheme 35.27 Synthesis of (*R*)-tolterodine.

The enantioselective Pictet–Spengler reaction, known as the intramolecular F-C alkylation of imines, can be considered as a straightforward method for the preparation of enantioenriched tetrahydroisoquinolines and tetrahydro-β-carbolines building blocks (Scheme 35.9). Indeed, the group of Jacobsen has devoted intensive efforts to this field by means of hydrogen-bond donor catalysis with thiourea derivatives. Through an acyl-Pictet–Spengler reaction, promoted by thiourea **17**, they have successfully accomplished the total synthesis of (+)-yohimbine, a member of the monoterpenoid indole alkaloids with diverse biological activities (Scheme 35.28) [87]. In addition, a variation of the previous methodology made possible the synthesis of indolizidinones and quinolizidinones [22]. Thus, the use of hydroxylactam **106**, which is easily synthesized from tryptamine (**104**) and succinic anhydride, in an asymmetric Pictet–Spengler-type cyclization reaction catalyzed by thiourea **18** affords a very efficient and concise entry to (+)-harmicine (Scheme 35.28).



Scheme 35.28 The Pictet–Spengler reaction and natural products synthesis.

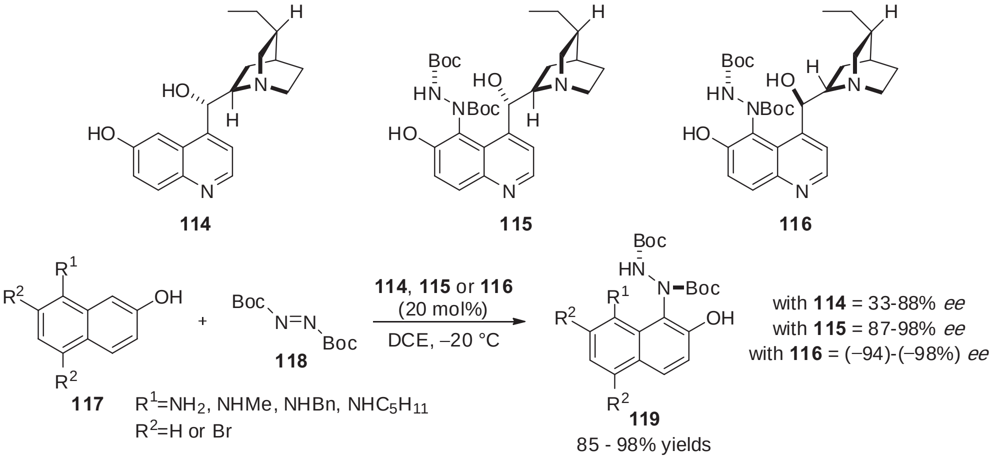
Enantioselective intramolecular F-C-type α-arylation of simple aldehydes, based on the concept of organo-SOMO catalysis, paved the way to the synthesis of two natural products via very sophisticated and well-designed strategies (Section 35.2.1). In 2009, Nicolaou and coworkers published the synthesis of the antitumor natural product demethyl calamenene [50] and, independently, in the same year the group of MacMillan developed an elegant route to (−)-tashiromine (Scheme 35.29) [5b].



Scheme 35.29 Natural products synthesis based on the SOMO-catalysis concept.

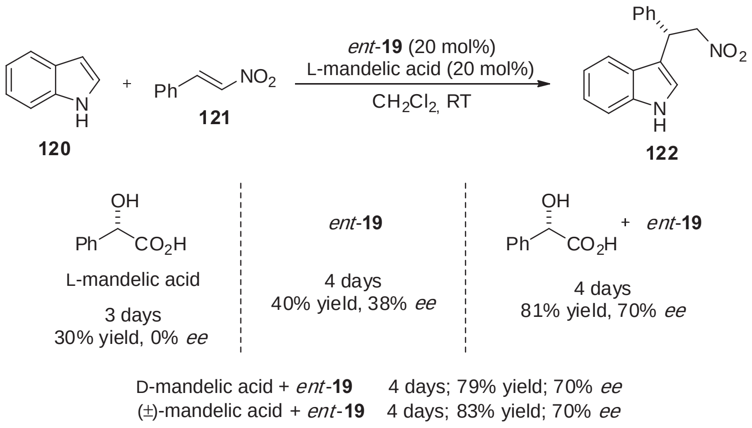
35.5 Miscellaneous

An elegant application of cinchona alkaloid derivatives in the F-C-type transformation was reported in 2006, in which azodicarboxylates were used as effective electrophiles, though unusually in this case [88]. Indeed, by using such electrophiles in aza-F-C-type alkylations we can expect to obtain the desired aminated products in an achiral form. Nevertheless, it has been shown that enantioselective F-C aminations of 8-amino-2-naphthol derivatives with azodicarboxylates thorough dihydrocupreidine **114**, a cinchona alkaloid derivative, give rise to a new family of non-biaryl atropisomers in good yields and up to 98% ee. In addition, they found that the catalyst itself can also act as a substrate for the F-C reaction, giving rise to novel cinchona alkaloid derivatives **115** and **116**. Surprisingly, these new compounds proved to be suitable for promoting the F-C alkylations between 8-amino 2-naphthol analogs **117** and azodicarboxylates, furnishing the desired products with higher enantioselectivities compared with **114** (Scheme 35.30).



Scheme 35.30 Novel non-biaryl atropisomers via asymmetric F-C amination.

The combination of a Brønsted acid additive with a chiral thiourea catalyst was used to mediate F-C alkylation between indoles and nitroolefins [89]. In this study, a synergic effect was shown as both species together gave a higher effect than each one separately (Scheme 35.31). Interestingly, the authors observed that the enantioselection of the reaction is mainly governed by the thiourea catalyst, as the use of L-, D-, or (±)-mandelic acid as additive gives the same enantiomeric outcome. The results obtained within this work could not only be the starting point for the development of research related to the effect of additives in thiourea-mediated catalysis but also to other dual-organocatalytic systems to achieve appropriate assembly and higher catalytic efficiency.



Scheme 35.31 Mandelic acid-assisted F-C alkylation with thiourea *ent*-**19**.

35.6
Conclusion

Throughout this chapter, selected examples of organocatalyzed asymmetric F-C reactions have been presented. Since 2001, when pyrroles and indoles were found to successfully undergo electrophilic aromatic alkylations in the presence of imidazolidinones, the organocatalyzed F-C reaction has become a powerful tool for the asymmetric functionalization of aromatic and heteroaromatic nuclei, ranking among the most effective methods for C–C and C–N bond formation. Mostly, two types of activation are observed: activation via iminium/enamine catalysis (which is mainly achieved via primary or secondary chiral amines with α,β-unsaturated enals or enones) and activation through hydrogen-bond formation (in the presence of chiral phosphoric acids, thioureas, etc). Notably, the recently introduced concept of SOMO-catalysis has also been used to achieve highly selective organocatalyzed F-C alkylations with simple aldehydes. Among the different classes of electrophiles that were used to carry out such transformations, emphasis might be given to the α,β-unsaturated enals or enones, nitroolefins, carbonylated compounds, and imines (aza-F-C reaction). Concerning aromatic nucleophiles, until recently, examples mainly involved indole and pyrrole analogs and the use of less electron-rich aromatic rings was scarcely reported. In the last two years, efforts in organocatalyzed F-C reactions have focused on broadening the scope not only for the aromatic nucleophile partner but also for the electrophile scaffold. Novel activation strategies that could extend the scope of these reactions are also the subject of extensive research.

In general, the new stereocenters created in the C–C or C–N bond formation process possess a high degree of enantioselectivity and the products are obtained in high yields. Moreover, in some remarkable examples it has been shown that to engage F-C-type alkylation in organocascade process renders possible the synthesis of very complex molecular entities. In addition, the total synthesis of natural products or pharmaceutically interesting building blocks could be achieved, affording the targeted products in high yields and selectivities by means of more concise strategies (fewer steps compared with previous reported syntheses).

Undoubtedly, since seminal contributions in 2001, organocatalyzed asymmetric F-C-type alkylation can be considered as a tool of paramount importance for C–C and C–N bond formation in electrophilic aromatic substitutions and one of the most outstanding applications of organocatalysis in the field of organic chemistry.

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Part IV
Ring-Forming Reactions

36
Intramolecular Reactions

You-Cai Xiao and Ying-Chun Chen

36.1
Introduction

Organocatalysis has emerged as a powerful synthetic paradigm that is complementary to metal-catalyzed transformations and has facilitated the development of new methods to make various chiral molecules [1, 2]. It has also attracted great interest in organic chemistry for its potential applications in total synthesis [3].

Among the variety of organic transformations that are amenable to organocatalysis, the ring-forming reactions occupy a predominant position for efficient constructions of chiral carbo- and heterocycles [4]. In fact, the L-proline-catalyzed intramolecular asymmetric aldol reaction of a triketone compound was reported by two industrial research groups as early as 1971 [5].

This chapter will discuss organocatalytic intramolecular ring-forming reactions, and is organized according to the different types of catalytic mechanisms: covalent catalysis (enamine, iminium, SOMO, carbene, and Lewis basic tertiary amine or phosphine catalysis) and non-covalent catalysis (Brønsted acid catalysis and bifunctional catalysis). Notably, stoichiometric or non-asymmetric examples are not discussed here. Important catalytic reactions exhibiting high enantioselectivity and wide applications in organic synthesis have been selected and highlighted in schemes. We hope that this layout will benefit readers who wish to gain initial information quickly by browsing through this chapter. Most of the reaction mechanisms are not covered since they are already discussed in detail elsewhere. The coverage of the present chapter generally extends to December 2011.

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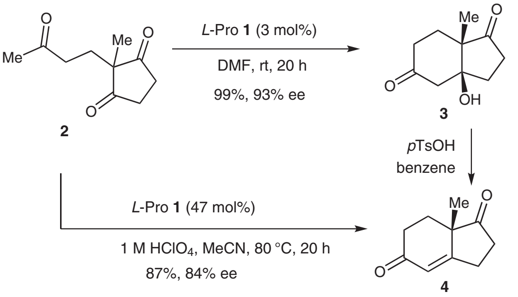
36.2
Intramolecular Ring-Forming Reactions via Covalent Catalysis

36.2.1
Enamine Catalysis

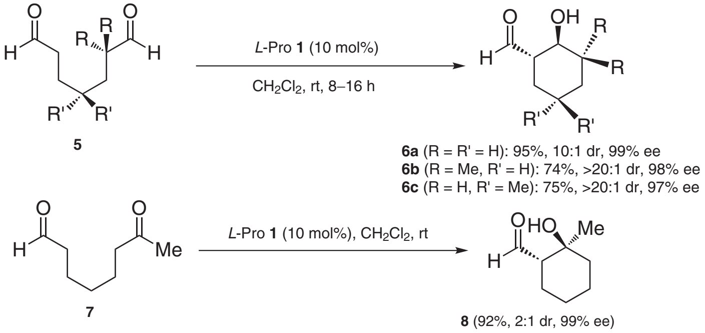
Many important intramolecular reactions, such as aldol reaction, Michael addition, transannular reaction, and α-alkylation reaction, could be realized via enamine catalysis.

In 1971, Hajos and Wiechert independently reported intramolecular desymmetrization cyclization via the aldol reaction. Hajos mentioned that the intramolecular aldol reaction of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (**2**) could smoothly afford bicyclic diketone **3** catalyzed by L-proline (**1**) in *N,N*-dimethylformamide (DMF), in excellent yield and with 93% ee. Further dehydration of **3** yielded the unsaturated diketone **4** (Scheme 36.1) [5a]. In Wiechert's work, diketone **4** could be obtained directly from **2** by employing perchloric acid in refluxing acetonitrile (Scheme 36.1) [5b].



Scheme 36.1 L-Proline-catalyzed desymmetrization aldol reaction.

In contrast to the early report of intramolecular desymmetrization reactions [6], the intramolecular ring-closing reactions of achiral substrates via enamine catalysis were not disclosed until the beginning of the twenty-first century. In 2003, List reported the first highly stereoselective intramolecular aldol reaction of achiral dicarbonyl compounds. Cyclic aldol products **6a–c** were delivered from heptanedials **5** with excellent diastereo- and enantioselectivity by the catalysis of L-proline (Scheme 36.2). The cyclization of ketoaldehyde **7** afforded alcohol **8** as a 2 : 1 diastereomeric mixture but with 99% ee. This strategy could provide β-hydroxyl carbonyl derivatives that are of potential applications in organic synthesis [7a].



5

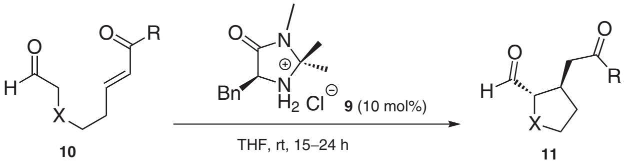
6a (R = R' = H): 95%, 10:1 dr, 99% ee
6b (R = Me, R' = H): 74%, >20:1 dr, 98% ee
6c (R = H, R' = Me): 75%, >20:1 dr, 97% ee

7

8 (92%, 2:1 dr, 99% ee)

Scheme 36.2 L-Proline-catalyzed intramolecular aldol reaction.

Subsequently, List reported the first organocatalytic intramolecular Michael reaction of multifunctional aldehydes **10**. Although this reaction could also be catalyzed by L-proline, both diastereo- and enantioselectivity were low. MacMillan's chiral imidazolidinone **9** gave much better results and the cyclic ketoaldehydes **11** could be obtained efficiently (Scheme 36.3) [8a].



10

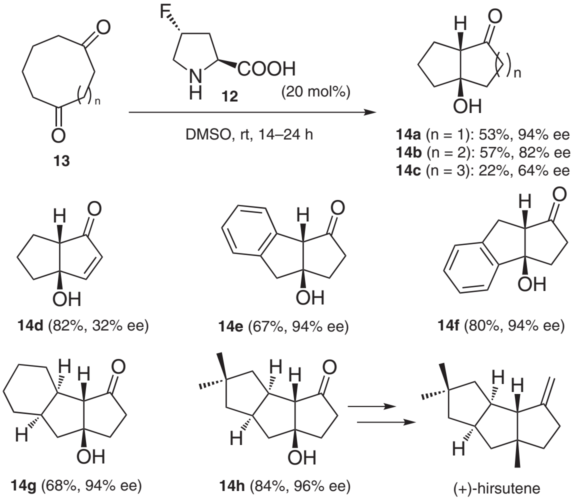
X = CH_2, NTs
R = H, Me, Et, Benzyl, 2-Naphthyl

11

6 examples
85–99%, 8:1–49:1 dr
80–97% ee

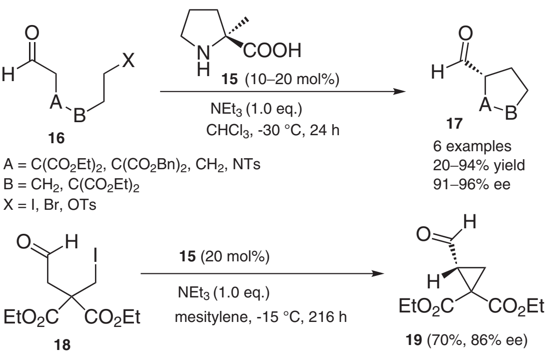
Scheme 36.3 Asymmetric intramolecular Michael reaction.

The organocatalytic asymmetric transannular aldolization, which could create two new rings and at least two new stereogenic centers, was also developed by List and coworkers [9a]. After testing several proline derivatives, the authors found that *trans*-4-fluoro-proline **12** was able to catalyze the aldol reaction of 1,4-cyclooctanediones **13**. Various polycyclic products **14** were obtained in good yields and with high enantioselectivity. Furthermore, product **14h** was efficiently transformed into (+)-hirsutene, a popular synthetic target, by means of a short three-step sequence (Scheme 36.4).



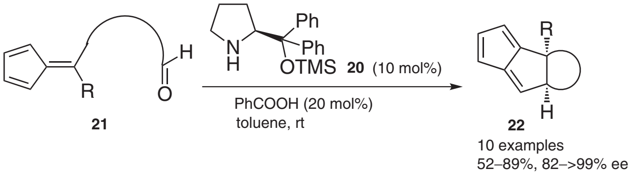
Scheme 36.4 Asymmetric transannular aldol reaction.

The α-alkylation of carbonyl compounds is a key carbon–carbon bond forming reaction in organic chemistry. Despite the widespread applications of this method, a general asymmetric intramolecular α-alkylation via enamine catalysis has proven to be extremely challenging because of catalyst alkylation, or racemization of products in the reaction. List and coworkers developed an intramolecular α-alkylation of aldehydes by using (*S*)-α-methylproline (**15**) as the catalyst [10]. To eliminate the influence of the by-product HX, a stoichiometric amount of NEt_3 was added. A diversity of chiral cyclopentanes and pyrrolidines **17**, or cyclopropanes **19**, could be obtained in high yields and ees (Scheme 36.5).



Scheme 36.5 Organocatalytic intramolecular α-alkylation of aldehydes.

Recently, Hayashi and coworkers reported the first example of an organocatalytic intramolecular [6+2] cycloaddition reaction of fulvenes via enamine catalysis of secondary amine **20**. The authors found that cycloaddition of fulvenes **21**, which have a δ-formylalkyl group at the exocyclic 6-position, could provide the cis-fused triquinane derivatives **22** in moderate yields and with excellent enantioselectivity (Scheme 36.6). Computational investigation of this reaction suggests a concerted mechanism via a highly asynchronous transition state [11].

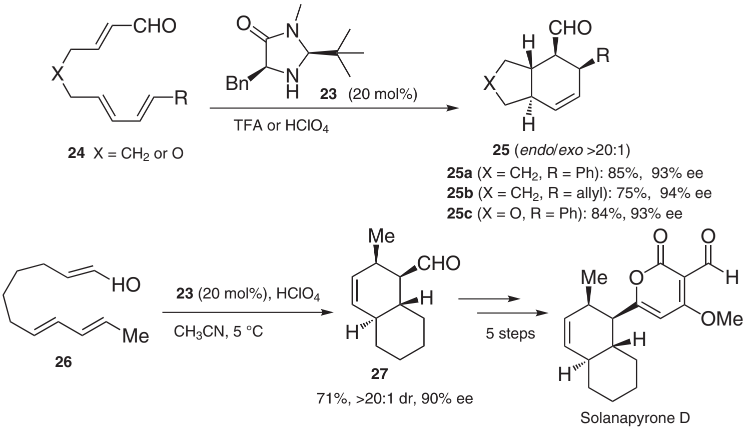


Scheme 36.6 Organocatalytic intramolecular [6+2] cycloaddition.

36.2.2
Iminium Catalysis

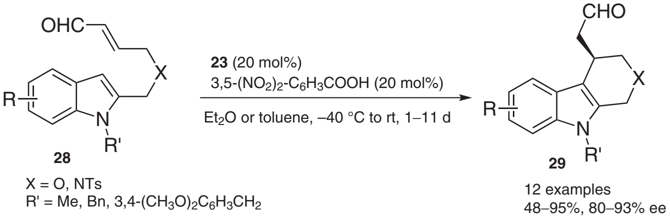
Iminium catalysis is another key catalytic concept in aminocatalysis. Initial work was disclosed by MacMillan for the Diels–Alder reaction of cyclopentadiene and α,β-unsaturated aldehydes [12], but it was rapidly extended to Michael additions (including Friedel–Crafts reactions). Now iminium catalysis has been established as a general mode for nucleophilic addition to α,β-unsaturated carbonyl compounds.

The first asymmetric organocatalytic intramolecular Diels–Alder reaction was reported by MacMillan in 2005. This LUMO-lowering organocatalytic strategy proved to be effective for the enantioselective Diels–Alder reaction of a range of trienal substrates **24**. In the presence of imidazolidinone catalyst **23**, the cycloadducts **25** could be attained in good yields and with excellent enantio- and diastereoselectivity. Moreover, the authors applied this strategy to the rapid total synthesis of marine metabolite solanapyrone D (Scheme 36.7) [13].



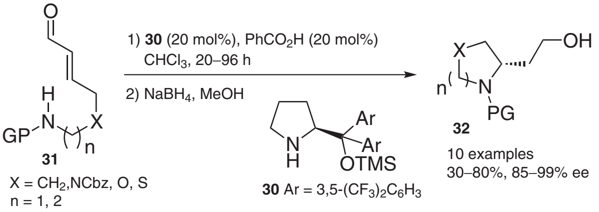
Scheme 36.7 Organocatalytic intramolecular Diels–Alder reaction.

Xiao reported an intramolecular Friedel–Crafts reaction using the same imidazolidinone catalyst [14a]. This method allowed direct access to tetrahydropyrano [3,4-*b*]indoles or tetrahydro-β-carbolines **29** from simple α,β-unsaturated aldehydes **28** in good yields and with high enantioselectivity (Scheme 36.8).


OHC
R
X
N
R'
28
X = O, NTs
R' = Me, Bn, 3,4-(CH3O)2C6H3CH2
23 (20 mol%)
3,5-(NO2)2-C6H3COOH (20 mol%)
Et2O or toluene, –40 °C to rt, 1–11 d
CHO
29
12 examples
48–95%, 80–93% ee

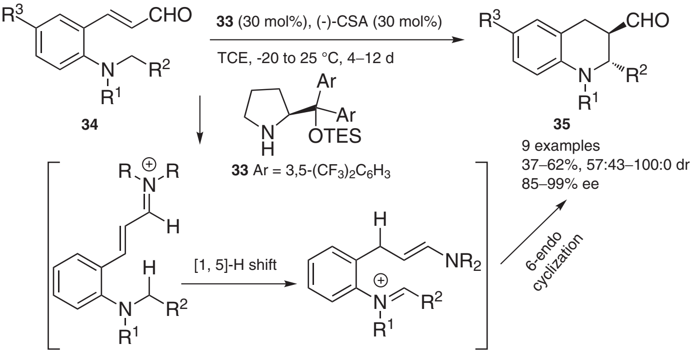
Scheme 36.8 Organocatalytic intramolecular Friedel–Crafts reaction.

Conjugated aza-addition to α,β-unsaturated compounds constitutes one of the most important methods in C–N bond forming reactions. It was not until 2007 that the highly stereocontrolled intramolecular aza-Michael addition was disclosed via iminium catalysis [15a]. The reaction of carbamates **31** bearing an α,β-unsaturated aldehyde moiety took place with good yields and excellent ees by catalysis of Jørgensen's catalyst **30**. This process provides an efficient way for the enantioselective preparation of several five- and six-membered heterocycles **32** (Scheme 36.9).



Scheme 36.9 Organocatalytic intramolecular aza-Michael reaction.

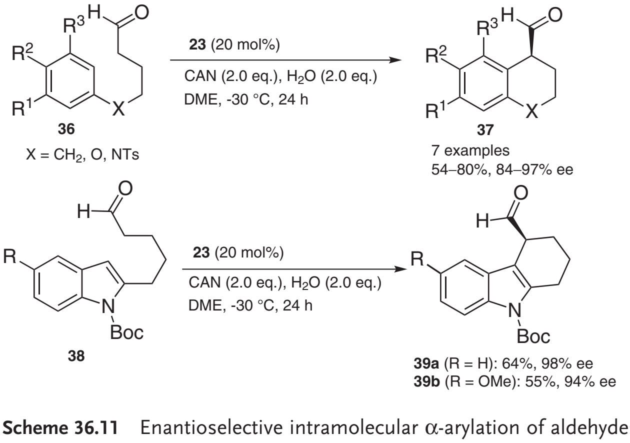
The rapid development of organocatalysis impels chemists to discover new synthetic methodologies. Many important transformations that could only be realized by transition metal catalysis can now be achieved via organocatalysis. In 2010, Kim and coworkers reported a novel C–H bond functionalization reaction via a tandem 1,5-hydride transfer/ring closure sequence. Based on the iminium–enamine cascade activation of catalyst **33**, the fused tetrahydroquinolines **35** could be synthesized from substrates **34** with good stereoselectivity. This is the first example of an organocatalytic intramolecular redox reaction (Scheme 36.10) [16].



Scheme 36.10 Organocatalytic stereoselective hydride transfer/ring closure sequence.

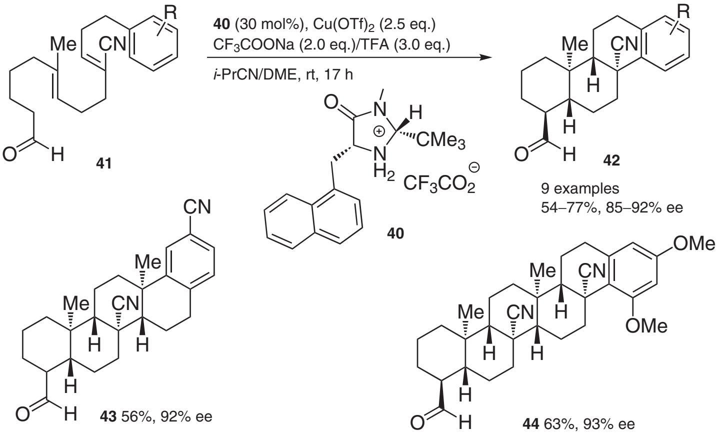
36.2.3
SOMO Catalysis

SOMO catalysis, which has been the subject of considerable attention in recent years, is a unique and versatile activation mode that can participate in bond construction with various π-rich nucleophiles. The first asymmetric intramolecular α-arylation of aldehydes was reported by Nicolaou in 2009 using organo-SOMO catalysis [17a]. The authors applied imidazolidinone **23** as catalyst and cerium ammonium nitrate (CAN) as the oxidant. Various 5-oxopentylbenzenes **36**, or indole derivatives **38**, could furnish the cyclic products **37** or **39**, respectively, in good yields and with excellent ees (Scheme 36.11). Later, MacMillan disclosed similar research [17b], and a theoretical study of the intramolecular α-arylation of aldehydes was also reported by the same group via density functional theory [17c].



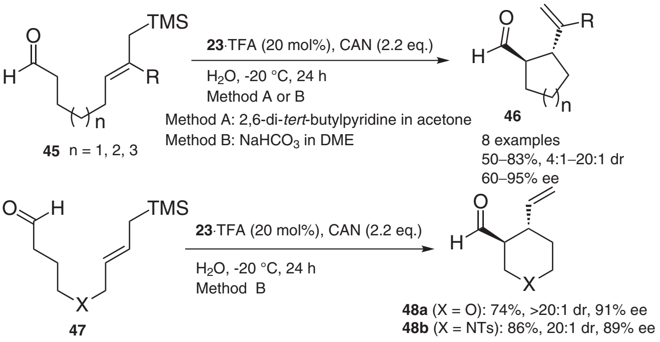
Scheme 36.11 Enantioselective intramolecular α-arylation of aldehydes.

Organo-SOMO catalysis was also applied to polyene cyclization. In 2010, MacMillan reported an enantioselective cyclization reaction of substrates **41** for accessing steroidal and terpenoidal frameworks. They used imidazolidinone **40** instead of catalyst **23**, with the aid of copper(II) triflate as the oxidant. The polyene cyclization took place smoothly, giving polycyclic systems **42** and even more complex compounds **43** or **44** in good yields and with high enantioselectivity and exclusive diastereoselectivity (Scheme 36.12) [18].



Scheme 36.12 Enantioselective polyene cyclization via organo-SOMO catalysis.

Recently, the intramolecular asymmetric α-allylation of aldehydes has also been accomplished by the MacMillan group via SOMO catalysis. As outlined in Scheme 36.13, this new enantioselective α-formyl cyclization can be employed to build five-, six-, and seven-membered carbocyclic rings **46** from aldehydes **45** in good yields and with a high level of stereocontrol. Heterocycles such as tetrahydropyran **48a** and piperidine **48b** could also be obtained from substrates **47** in a similar way [19].

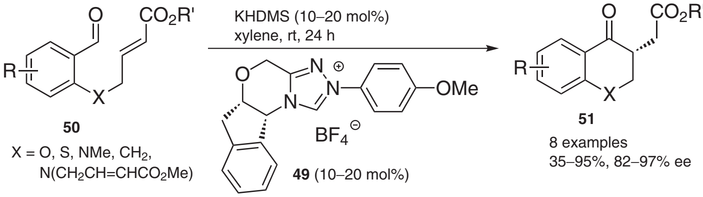


45 n = 1, 2, 3
23·TFA (20 mol%), CAN (2.2 eq.)
H$_2$O, -20 °C, 24 h
Method A or B
Method A: 2,6-di-*tert*-butylpyridine in acetone
Method B: NaHCO$_3$ in DME
46
8 examples
50–83%, 4:1–20:1 dr
60–95% ee
47
23·TFA (20 mol%), CAN (2.2 eq.)
H$_2$O, -20 °C, 24 h
Method B
48a (X = O): 74%, >20:1 dr, 91% ee
48b (X = NTs): 86%, 20:1 dr, 89% ee

Scheme 36.13 Intramolecular asymmetric α-allylation of aldehydes.

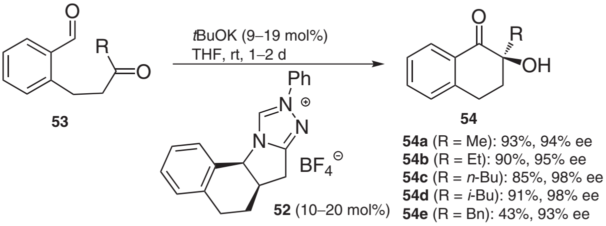
36.2.4
Carbene Catalysis

Carbenes belong to the most investigated reactive species in the field of organic chemistry. Besides their role as excellent ligands in metal-based catalytic reactions, organic carbene catalysis has emerged as an exceptionally fruitful research area. In 2002, Rovis reported a highly enantioselective intramolecular Stetter reaction of unsaturated esters **50** derived from salicylaldehyde by the catalysis of chiral aminoindanol-derived triazolium salt **49** (Scheme 36.14) [20a].



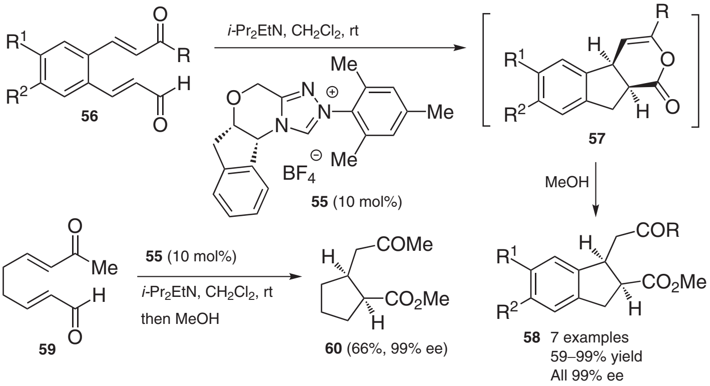
Scheme 36.14 Enantioselective intramolecular Stetter reaction.

In 2006, Enders reported an intramolecular cross benzoin reaction of bifunctional substrates **53** containing aldehyde and ketone groups to give various six-membered cyclic acyloins **54** in moderate to good yields. Up to 98% ee has been obtained upon catalysis by the tetracyclic triazolium salt **52** (Scheme 36.15) [21a]. Suzuki also developed a similar intramolecular asymmetric cross benzoin reaction [21b].


tBuOK (9–19 mol%)
THF, rt, 1–2 d
53
52 (10–20 mol%)
54
54a (R = Me): 93%, 94% ee
54b (R = Et): 90%, 95% ee
54c (R = n-Bu): 85%, 98% ee
54d (R = i-Bu): 91%, 98% ee
54e (R = Bn): 43%, 93% ee

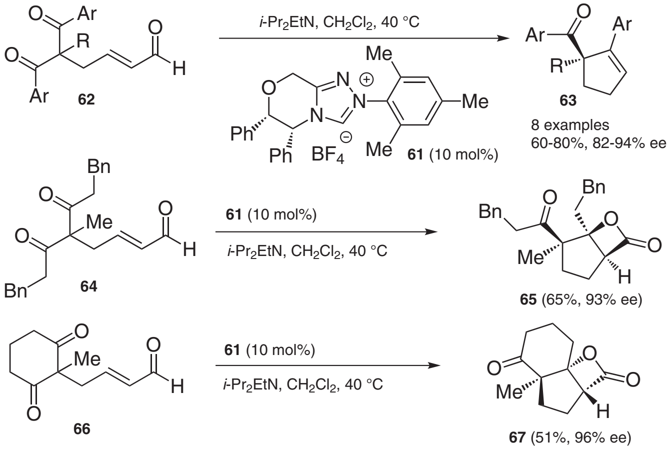
Scheme 36.15 Asymmetric intramolecular cross benzoin reaction.

As well as the traditional benzoin and Stetter reactions, some new synthetic transformations were disclosed via carbene catalysis. In 2007, the Scheidt group developed an intramolecular Michael-type reaction with unsaturated substrates **56** through catalysis with chiral triazolium salt **55**. The intermediates **57** were generated via a domino Michael addition/lactonization sequence, and bicyclic products **58** were afforded in satisfactory yields and with excellent enantioselectivity after *in situ* treatment with MeOH. A chiral cyclopentane **60** was similarly delivered from substrate **59** (Scheme 36.16) [22].



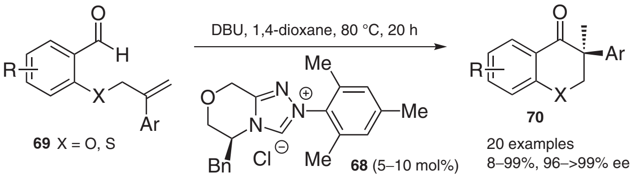
Scheme 36.16 Chiral carbene-catalyzed intramolecular Michael-type reaction.

Scheme and coworkers also reported an enantioselective desymmetrization reaction of 1,3-diketones **62** in the presence of triazolium salt **61**. This new process combines an intramolecular aldol reaction followed by a decarboxylation process of β-lactone intermediates, giving chiral cyclopentenes **63** in moderate yields and with high ees. Notably, with aliphatic diketones **64** or **66**, β-lactone products **65** or **67**, respectively, were obtained (Scheme 36.17) [23].



Scheme 36.17 Carbene-catalyzed desymmetrization of 1,3-diketones.

Recently, Glorius reported an elegant asymmetric hydroacylation of unactivated alkenes via carbene catalysis [24]. Chromanone derivatives **70** containing an all-carbon based quaternary stereocenter could be efficiently produced from simple 2-allyloxybenzaldehydes **69**. Good yields and excellent enantioselectivity were obtained in the presence of chiral triazolium salt **68** and DBU. In addition, quantum-chemical calculations support a concerted but very asynchronous transition state (Scheme 36.18).

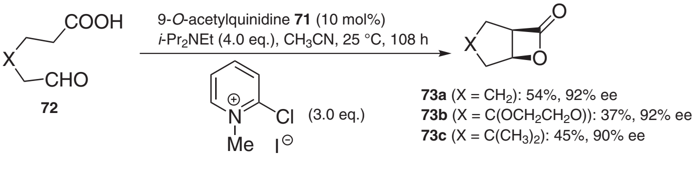


Scheme 36.18 Enantioselective hydroacylation of unactivated olefins.

36.2.5

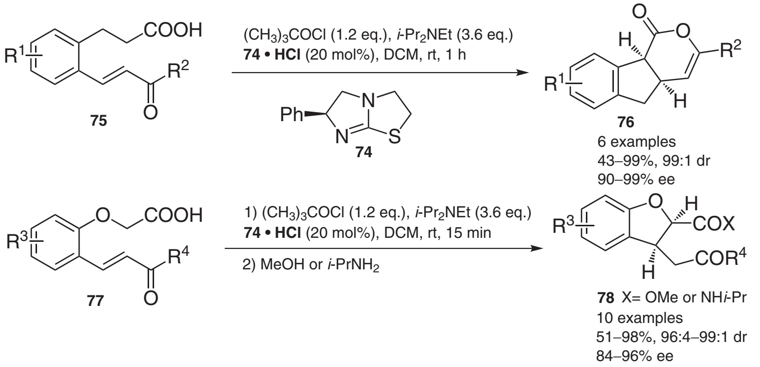
Lewis Base Catalysis of Tertiary Amines or Phosphines

Lewis base or nucleophilic catalysis of chiral tertiary amines or phosphines has been widely exploited in organocatalysis. In 2001, Romo reported an asymmetric aldol/lactonization reaction with substrates **72** by using cinchona alkaloids as the catalyst. Bicyclic β-lactones **73** were obtained in moderate yields and excellent enantioselectivity catalyzed by 9-*O*-acetylquinidine (**71**) (Scheme 36.19) [25a]. Later, the same group extended this strategy to the highly enantioselective intramolecular aldol/lactonization reaction involving the use of homobenzotertramisole as catalyst. [25b].


9-O-acetylquinidine 71 (10 mol%)
i-Pr2NEt (4.0 eq.), CH3CN, 25 °C, 108 h
72
(3.0 eq.)
73a (X = CH2): 54%, 92% ee
73b (X = C(OCH2CH2O)): 37%, 92% ee
73c (X = C(CH3)2): 45%, 90% ee

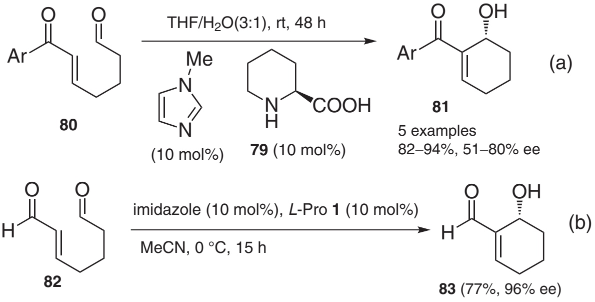
Scheme 36.19 Organocatalytic intramolecular aldol/lactonization reaction.

The Smith group, in 2011, developed a highly diastereo- and enantioselective intramolecular Michael addition/lactonization reaction. The authors applied a chiral tetramisole (**74**) to catalyze the cyclization of multifunctional substrates **75** or **77**, affording fused indanes **76** or dihydrobenzofuran carboxylates **78**, respectively, in good yields and with excellent ees (Scheme 36.20) [26].


(CH3)3COCl (1.2 eq.), i-Pr2NEt (3.6 eq.)
74 • HCl (20 mol%), DCM, rt, 1 h
75
74
76
6 examples
43–99%, 99:1 dr
90–99% ee
1) (CH3)3COCl (1.2 eq.), i-Pr2NEt (3.6 eq.)
74 • HCl (20 mol%), DCM, rt, 15 min
2) MeOH or i-PrNH2
77
78 X= OMe or NHi-Pr
10 examples
51–98%, 96:4–99:1 dr
84–96% ee

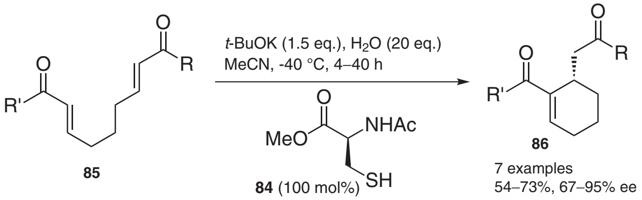
Scheme 36.20 Organocatalytic intramolecular Michael addition/lactonization reaction.

The Morita–Baylis–Hillman (MBH) reaction is a powerful carbon–carbon bond-forming reaction that has found widespread application in organic synthesis. In 2005, Miller and Hong independently reported the highly enantioselective intramolecular MBH reaction. The Miller group applied a combination of (*S*)-pipecolic acid **79** and *N*-methylimidazole to catalyze the cyclization of heptenal derivatives **80** in aqueous THF (Scheme 36.21a) [27a]. In contrast, Hong and coworkers used simple L-proline and imidazole as the catalysts (Scheme 36.21b) [27b].



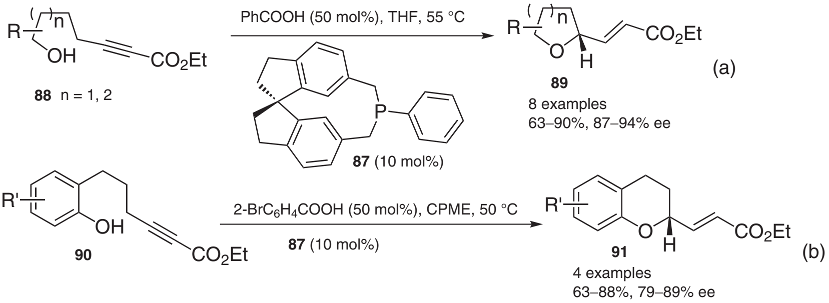
Scheme 36.21 Organocatalytic intramolecular MBH reaction.

Miller disclosed the first enantioselective intramolecular Rauhut–Currier reaction (also called vinylogous MBH reaction). A stoichiometric amount of protected cysteine derivative **84** and potassium *tert*-butoxide (1.5 eq.) were employed, and various bis-enones **85** were converted into cyclohexene products **86** in good yields and with high enantioselectivity (Scheme 36.22). Using a lower loading of **84** leads to a reduced yield but nearly identical ee [28a].



Scheme 36.22 Enantioselective intramolecular Rauhut–Currier reaction.

Phosphines serve as nucleophilic catalysts for several chemical transformations. The Fu group in 2009 developed an intramolecular vinylogous alkylation with hydroxyl-2-alkynoates **88**. Chiral spirocyclic phosphine **87** efficiently catalyzed this reaction, giving tetrahydrofurans or tetrahydropyrans **89** in good yields and ee values (Scheme 36.23a). The same group extended this methodology to the asymmetric synthesis of dihydrobenzopyrans **91** with 2-alkynoates **90** bearing a pendant phenol group (Scheme 36.23b) [29].

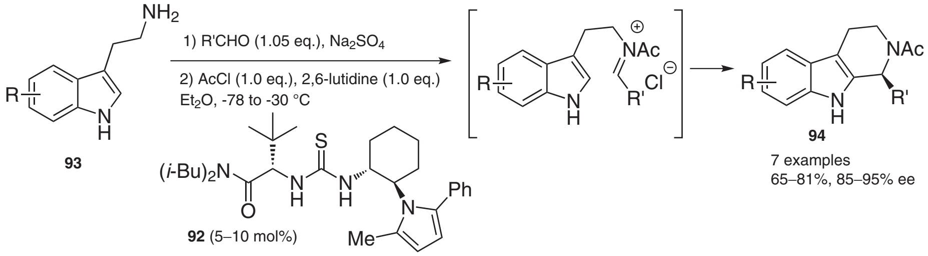


Scheme 36.23 Phosphine-catalyzed enantioselective cyclization of hydroxyalkynoates.

36.3
Intramolecular Ring-Forming Reactions by Non-Covalent Catalysis

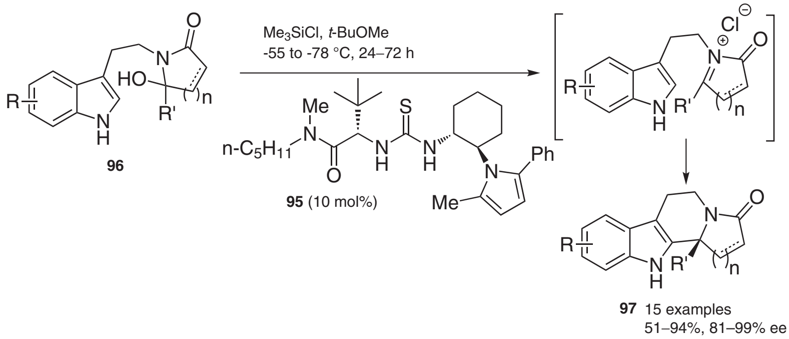
36.3.1
Brønsted Acid Catalysis

Enantioselective synthesis with chiral hydrogen-bonding donors has emerged as a frontier of research in the field of asymmetric catalysis. Jacobsen disclosed a successful intramolecular acyl-Pictet–Spengler reaction via hydrogen-bonding activation [30a]. Owing to the low reactivity of the imine substrate, the authors applied a more reactive *N*-acyl iminium ion formed *in situ* to access a range of *N*-acetyl-β-carbolines **94** through catalysis with chiral thiourea **92**, and, generally, high enantioselectivities were obtained (Scheme 36.24).



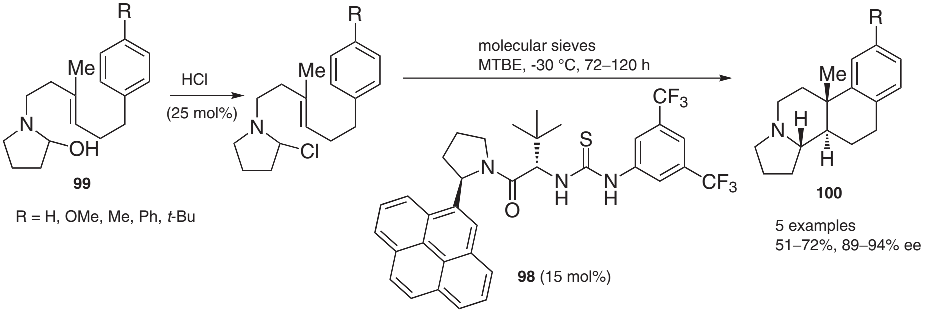
Scheme 36.24 Organocatalytic acyl-Pictet–Spengler reaction.

Subsequently, the Jacobsen group extended this strategy to the asymmetric Pictet–Spengler-type cyclization of hydroxylactams **96**. In the presence of chiral thiourea **95**, the reaction took place smoothly upon addition of the acidic additive trimethylsilyl chloride (Me_3SiCl), leading to highly enantioenriched indolizidinones **97** in moderate to good yields and with high enantioselectivity (Scheme 36.25). The mechanism of this reaction involves the formation of a *N*-acyliminium chloride–thiourea complex [31a].



Scheme 36.25 Asymmetric Pictet–Spengler cyclization of hydroxylactams.

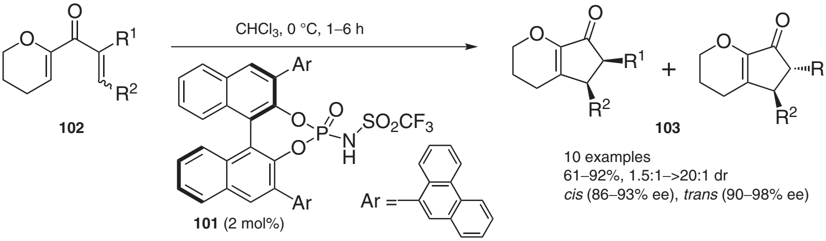
Inspired by the previous work, the Jacobsen group further developed the enantioselective cationic polycyclization. After careful studies on the reaction conditions, the authors selected chiral thiourea catalyst **98** for the asymmetric cyclization of hydroxylactams **99**, affording the products **100** in good yields and with excellent enantioselectivity (Scheme 36.26) [32].



Scheme 36.26 Enantioselective thiourea-catalyzed cationic polycyclization.

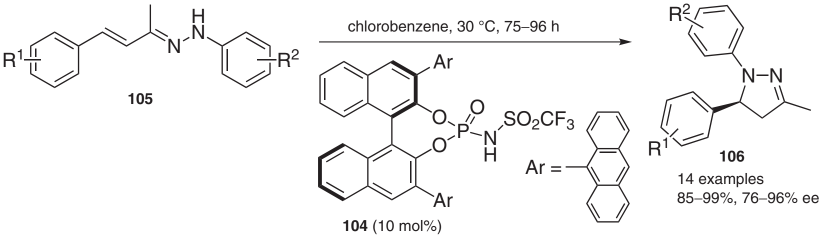
Stronger chiral Brønsted acid catalysts, especially phosphoric acids independently developed by Terada and Akiyama, have been extensively used to activate a C=X bond (X=O, NR, CR_2), thereby decreasing its LUMO energy and promoting nucleophilic addition to the C=X bond. Many synthetically useful intramolecular transformations have been developed with this activation strategy, including aldol and Michael reactions [33] and Pictet–Spengler and related reactions [34].

The Nazarov reaction belongs to a type of 4π electrocyclization and can usually be promoted by metal-based catalysts. In 2007, the first enantioselective organocatalytic Nazarov reaction was reported by Rueping and coworkers [35a]. A chiral *N*-triflyl-phosphoramide **101** was a better selection for the cyclization of dienone substrates **102**, and cyclopentenone products **103** were generated as a diastereomeric mixture but with excellent enantioselectivity at low catalyst loadings (2 mol%) (Scheme 36.27).



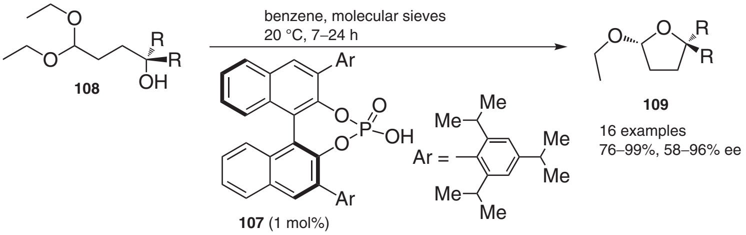
Scheme 36.27 Enantioselective Brønsted acid-catalyzed Nazarov cyclization.

Next, another work on a Brønsted acid-catalyzed intramolecular electrocyclization reaction was reported by List [36]. They demonstrated that chiral Brønsted acid **104** could efficiently promote the cycloisomerization of α,β-unsaturated hydrazones **105** to give pyrazolines **106** in high yields and with good enantioselectivity (Scheme 36.28). This is also the first example of an organocatalytic asymmetric 6π electrocyclization reaction.



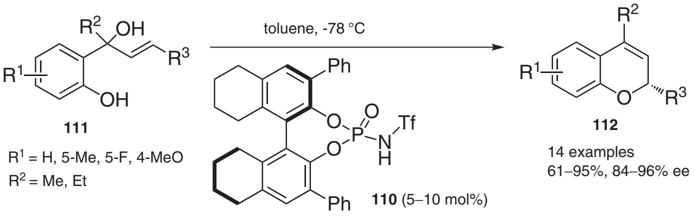
Scheme 36.28 Organocatalytic asymmetric 6π electrocyclization.

In 2010, List reported a catalytic enantioselective intramolecular trans-acetalization reaction via Brønsted acid catalysis [37a]. Chiral *O,O*-acetals, which are usually synthesized by enzymatic resolutions or metal-catalyzed desymmetrizations, could now be easily obtained by catalysis with phosphoric acid **107**. Alcohols **108** with both aliphatic and aromatic substitutions are suitable substrates, furnishing the tetrahydrofurans **109** in high yields and enantioselectivity (Scheme 36.29).



Scheme 36.29 Enantioselective intramolecular trans-acetalization reaction.

Chiral ion-pair catalysis has gained great interest. Recent progress has been made by Rueping who developed an enantioselective intramolecular allylic substitution by ion-pair catalysis involving the use of chiral Brønsted acid **110**. This unprecedented methodology has broad substrate scope, giving the corresponding 2*H*-chromenes **112** in good yields and with excellent enantioselectivity from substrates **111** (Scheme 36.30) [38].

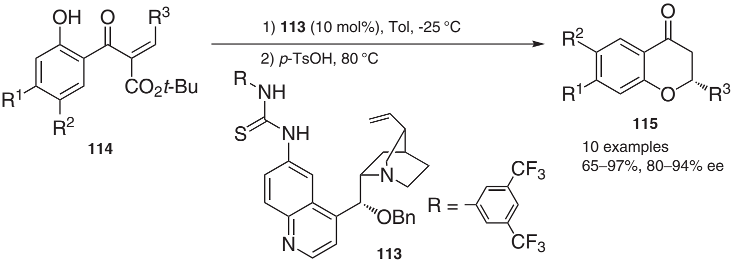


Scheme 36.30 Organocatalytic enantioselective allylic substitution.

36.3.2
Bifunctional Catalysis

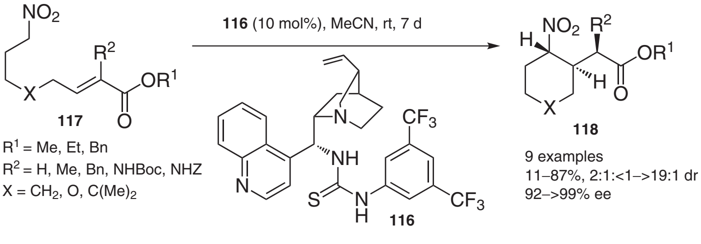
Bifunctional asymmetric catalysis, involving the synergistic activation of both acidic and basic sites in the substrates, has received great attention. The bifunctional catalysts discussed in this section generally contain a hydrogen-bond donor and a Brønsted basic moiety.

In 2007, Scheidt reported an intramolecular oxa-Michael reaction of α-substituted chalcones **114** catalyzed by cinchona alkaloid derived thiourea **113**. Chromanones **115** were efficiently produced after an acid-promoted decarboxylation process (Scheme 36.31) [39a].



Scheme 36.31 Enantioselective intramolecular oxa-Michael reaction.

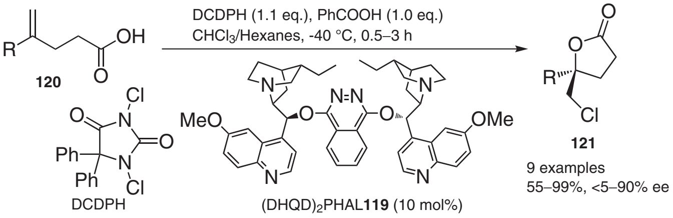
Cobb and coworkers reported another intramolecular Michael addition of conjugated esters **117**. They screened a range of thiourea catalysts and found bifunctional compound **116** gave satisfactory results in this cyclization, furnishing the cyclic γ-nitro esters **118** with up to three stereocenters (Scheme 36.32) [40].



Scheme 36.32 Stereoselective intramolecular Michael addition.

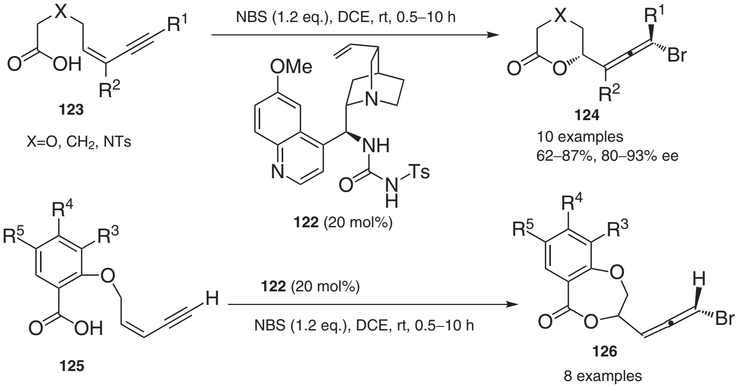
Although the field of organocatalysis has flourished over the past decade, there are still some areas that remain virtually untouched, such as the asymmetric α-halogenation of olefins. Several enantioselective halolactonization reactions of exocyclic carboxylic acids have been reported since 2010 [41]. Borhan and coworkers reported the first highly enantioselective chlorolactonization of alkenoic acids

120 by the catalysis with commercially available dimeric cinchona alkaloid $(DHQD)_2PHAL$ (**119**), giving γ-lactones **121** in low to excellent enantioselectivity (Scheme 36.33) [41a].



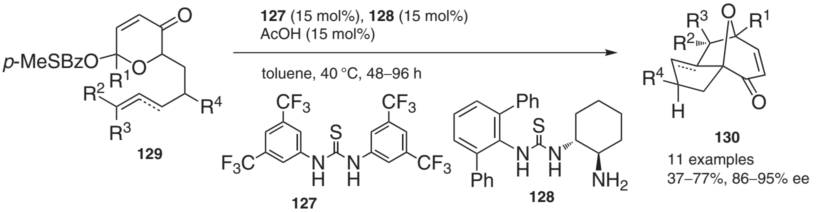
Scheme 36.33 $(DHQD)_2PHAL$-catalzyed asymmetric chlorolactonization.

Tang and coworkers reported a similar approach to the enantioselective bromolactonization of conjugated (*Z*)-enynes [42]. The bifunctional urea catalyst **122** promoted the cyclization of *cis*-enynes **123** or **125** with diverse substitutions, giving bromoallenes **124** or heterocycles **126**, respectively, in good yields and with high optical purity (Scheme 36.34).



Scheme 36.34 Enantioselective organocatalytic bromolactonization of *cis*-enynes (NBS = *N*-bromosuccinimide).

Recently, Jacobsen and coworkers disclosed a dual thiourea catalytic system that consists of an achiral thiourea (**127**) and a chiral primary aminothiourea (**128**) for an intramolecular oxidopyrylium [5+2] cycloaddition reaction. Valuable tricyclic structures **130** were obtained from substrates **129** in moderate yields and with high enantioselectivity (Scheme 36.35) [43].



Scheme 36.35 Enantioselective oxidopyrylium-based [5+2] cycloaddition.

36.4
Conclusion

As we can see from this chapter, the rapid development of organocatalysis makes the stereocontrolled construction of a huge variety of carbo- and heterocyclic compounds possible via intramolecular ring-forming reactions. Desymmetrization, ring-closing, cycloaddition, and annulation reactions are amenable via diverse organocatalytic strategies. Although several important intramolecular ring-forming reactions have been covered in this chapter, many useful ones have not been discussed due to page limitations and are only cited in reference section. This explosively growing field, without doubt, will continue to yield impressive results in the coming future.

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37

Formation of 3-, 4- and 5-Membered Cycles by Intermolecular Reactions

Hélène Pellissier

37.1

Introduction

The stereocontrolled construction of chiral five-, four-, and three-membered carbo- and heterocycles is a topic of paramount importance in modern organic synthesis, driven by the predominance of chiral mono- and polycyclic systems in natural products and in chiral pharmaceuticals [1]. While the end of the last century was dominated by the use of metal catalysis [2] and biocatalysis [3], a change in perception has occurred during the last 15 years, when several reports confirmed that relatively simple organic molecules could be highly effective and remarkably enantioselective catalysts of various fundamentally important transformations [4]. This rediscovery has initiated an explosive growth of research activities in organocatalysis, which presents advantages from an economical and environmental point of view [5]. Because of the absence of transition metals, organocatalytic methods, which are predominantly amine-based reactions [5q, 5u, 6], seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, such as pharmaceutical products [7]. Among the great variety of organic transformations that are amenable to asymmetric organocatalysis, intermolecular ring-forming reactions occupy a preeminent position, since they are of unique value for increasing molecular complexity and thereby achieving step brevity [8]. In particular, organocatalytic intermolecular formations of chiral five-, four-, and three-membered cycles, by virtue of allowing the regio- and stereoselective construction of new rings by simple addition of two molecules, occupy a leading position among the tools available to the synthetic chemist that best meet the above requirements.

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37.2
Organocatalytic Asymmetric Synthesis of Five-Membered Cycles

37.2.1
Synthesis of Five-Membered Cycles via [3+2] Cycloadditions

The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition [9], is a classic reaction in organic chemistry, consisting in the reaction of a dipolarophile with a 1,3-dipolar compound, allowing the production of various five-membered heterocycles [10]. This reaction represents one of the most productive fields of modern synthetic organic chemistry [11]. Most of the dipolarophiles are alkenes, alkynes, and molecules possessing related heteroatom functional groups (such as carbonyls and nitriles). The 1,3-dipoles can basically be divided into two different types, the allyl anion type such as nitrones, azomethine ylides, nitro compounds (bearing a nitrogen atom in the middle of the dipole), carbonyl ylides, or carbonyl imines (bearing an oxygen atom in the middle of the dipole) and the linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkanes, or azides. Two π-electrons of the dipolarophile and four electrons of the dipolar compound participate in a concerted pericyclic shift. The addition is stereoconservative (suprafacial), and the reaction is therefore a $[2_S+4_S]$ cycloaddition. In recent years, asymmetric 1,3-dipolar cycloadditions have become one of the most powerful tools for the construction of enantiomerically pure five-membered heterocycles [11a, 12]. Up to five stereocenters can be introduced in a stereoselective manner in only a single step. In addition, a range of different substituents can be included in the dipole and the dipolarophile, resulting in a broad range of possible cycloadducts, which can serve as useful synthetic building blocks.

37.2.1.1 [3+2] Cycloadditions of Nitrones

The 1,3-dipolar or [3+2] cycloaddition reaction of nitrones with dipolarophiles such as alkenes has received considerable attention in asymmetric synthesis over the past 20 years [12a, b, 13]. One of the reasons for the success of synthetic applications of nitrones is that, contrary to most other 1,3-dipoles, most nitrones are stable compounds that do not require *in situ* formation. Another synthetic utility of this reaction is the variety of attractive nitrogenated compounds that are available from the thus-formed isoxazolidines with up to three contiguous stereocenters, such as 1,3-aminoalcohols, amino acids, azasugars, and alkaloids. The first asymmetric organocatalytic 1,3-dipolar cycloaddition was reported by MacMillan *et al.*, in 2000 [14]. The authors disclosed that chiral imidazolidinone catalysts, such as **1** (Figure 37.1), promoted the reaction between enals and nitrones, by activating the double bond of the enal via iminium activation, affording the corresponding adducts in good yields (66–98%) and moderate to good diastereo- (62–98% de) and high enantioselectivities (90–99% ee). A few years later, chiral pyrrolidinium salts were employed by Karlsson and Hoedgberg as catalysts in the [3+2] cycloaddition of nitrones with 1-cycloalkene-1-carbaldehydes, providing the corresponding *exo*-bicyclic isoxazolidinones in good yields and diastereoselectivities combined with

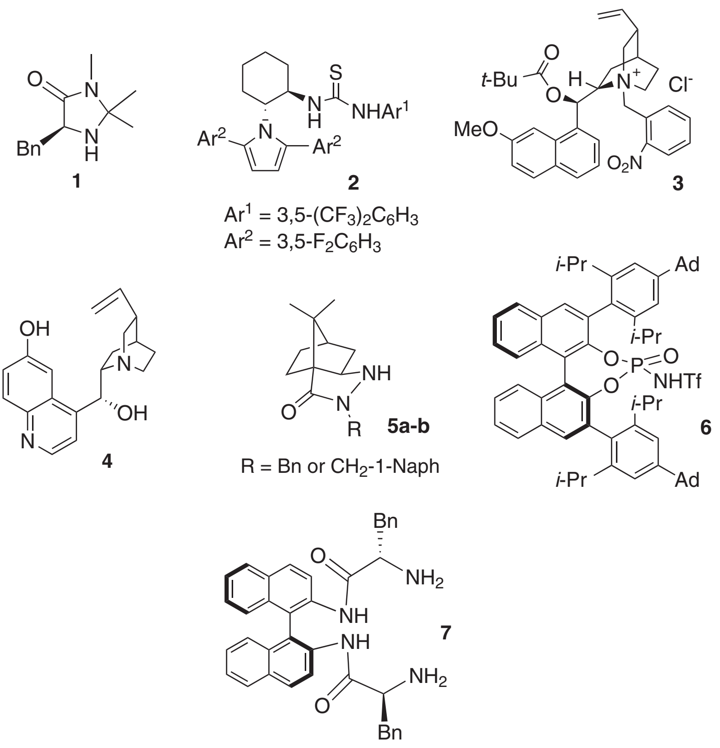
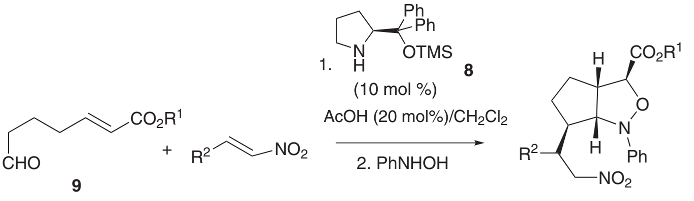


Figure 37.1 Organocatalysts used in [3+2] cycloadditions of nitrones. (Ad = adamantyl, Bn = benzyl, Naph = naphthyl, Tf = trifluoromethanesulfonyl.)

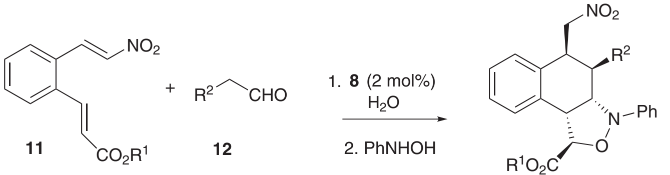
moderate enantioselectivities [15]. In 2004, Benaglia *et al.* developed a poly(ethylene glycol)-supported imidazolidinone catalyst that promoted the enantioselective dipolar cycloaddition of nitrones with enals in good yields and stereoselectivities [16]. In 2007, Cordova *et al.* reported a similar reaction promoted by diphenylprolinol derivatives, such as (*S*)-diphenylprolinol trimethylsilyl ether **8** [17]. In this work, the nitrones were prepared *in situ* by reaction of *N*-arylhydroxylamines with aldehydes, providing the corresponding cycloadducts in good yields and enantioselectivities of up to 99% ee. In the same year, Nevalainen *et al.* applied the triflate salt resulting from the treatment of **8** with trimethylsilyl triflate to catalyze the addition of nitrones to enals [18]. The corresponding isoxazolidines were achieved in high yields and excellent *endo*-diastereo- and enantioselectivities of up to 98% de and 96% ee, respectively. The scope of the reaction could be extended to 1-cyclopentene-1-carboxaldehyde, providing the corresponding fused isoxazolidines in good yields (66–75%) combined with good to high *endo*-selectivities (58–80% de) along with moderate to high enantioselectivities (37–83% ee). In 2009, Zhong *et al.* reported a highly stereoselective one-pot synthesis of bicyclic isoxazolidines bearing five stereogenic centers based on the reaction of 7-oxohept-2-enoates **9** with nitroolefins [19]. This cascade process involved a Michael addition/

nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition catalyzed by amine **8**. Thus, a series of bicyclic oxazolidines **10** were obtained in good to excellent yields with excellent diastereo- and enantioselectivities of up to 94% de and >99% ee, respectively (Scheme 37.1). As an extension of this methodology, these authors have reported another highly stereoselective Michael addition/nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition cascade reaction, involving various substituted 7-oxohept-2-enoates, hydroxyamines, and bis(phenylsulfonyl)ethylene as the reactants [20]. In the presence of catalyst **8**, the reaction afforded a single diastereomer of the corresponding indanes bearing four stereogenic centers in excellent yields and enantioselectivities of up to 99% ee. In addition, these authors have applied a closely related methodology with the Michael addition/nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition cascade process occurring between nitroolefin acrylates **11** and aldehydes **12** upon catalysis with the same catalyst [21]. In this case, the process was performed in



10

R^1 = Et, R^2 = Ph: 84% de = 94% ee >99%
R^1 = Et, R^2 = p-Tol: 81% de = 90% ee >99%
R^1 = Et, R^2 = p-ClC_6H_4: 83% de = 90% ee >99%
R^1 = Et, R^2 = p-FC_6H_4: 84% de = 90% ee >99%
R^1 = Et, R^2 = p-$NO_2C_6H_4$: 92% de = 90% ee >99%
R^1 = Et, R^2 = m-$MeOC_6H_4$: 79% de = 88% ee >99%
R^1 = Et, R^2 = o-$NO_2C_6H_4$: 73% de = 88% ee >99%
R^1 = Et, R^2 = 2-Fu: 81% de = 90% ee >98%
R^1 = Me, R^2 = n-Pr: 62% de = 78% ee >99%
R^1 = Me, R^2 = i-Pr: 51% de = 92% ee >99%



13

R^1 = Et, R^2 = n-Pr: 73% de = 96% ee >99%
R^1 = Et, R^2 = Et: 83% de = 96% ee >99%
R^1 = Et, R^2 = i-Pr: 48% de = 98% ee >99%
R^1 = Et, R^2 = $(CH_2)_5Me$: 71% de = 98% ee >99%
R^1 = Et, R^2 = Bn: 72% de = 96% ee >99%
R^1 = Et, R^2 = $(CH_2)_2OBn$: 51% de = 94% ee >99%
R^1 = Bn, R^2 = n-Pr: 63% de = 94% ee >99%
R^1 = R^2 = Bn: 73% de = 96% ee >99%
R^1 = Bn, R^2 = $(CH_2)_2OBn$: 73% de = 88% ee >99%

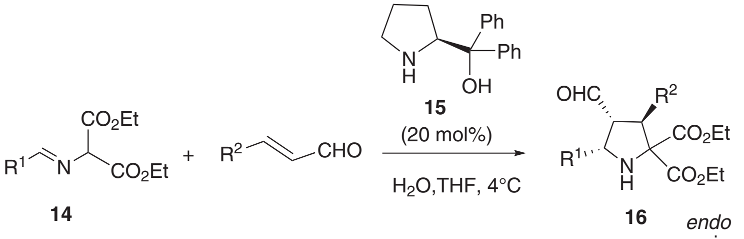
Scheme 37.1 Synthesis of bi- and tricyclic oxazolidines through Michael addition/nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition cascade reactions (Fu = furyl).

aqueous media and afforded a series of biologically significant, heavily functionalized, chiral tetrahydronaphthalenes **13** bearing five stereogenic centers with good to high yields combined with excellent diastereoselectivities of up to 98% de, while the enantioselectivity was >99% ee in all cases of substrates studied (Scheme 37.1).

In recent years, chiral thioureas have been investigated as organocatalysts in the [3+2] cycloaddition. The first organocatalytic asymmetric 1,3-dipolar cycloaddition of nitrones to β-alkyl nitroolefins was developed by Chen *et al.* by using novel chiral thiourea-pyrrole organocatalysts, such as **2** (Figure 37.1), giving rise to the corresponding chiral isoxazolidines in good yields of up to 93%, moderate to high enantioselectivities (40–88% ee), and excellent diastereoselectivities (>98% de) [22]. On the other hand, cinchona alkaloids have been successfully used as organocatalysts in [3+2] cycloadditions of *in situ* generated nitrones with various alkenes. Thus, Bernardi *et al.* have developed a novel [3+2] nitrone cycloaddition using *N*-Boc- and *N*-Cbz-protected *N*-hydroxy-α-amido sulfones as nitrone precursors [23]. In the presence of quinine-derived ammonium salt **3** (Figure 37.1) as catalyst, these unstable nitrones reacted with a series of glutaconates, giving access to the corresponding *N*-Boc- and *N*-Cbz-protected isoxazolidines in good yields and enantioselectivities of >99% ee. Remarkably, the cycloadducts were always obtained as single diastereomers. In 2010, Rodriguez *et al.* reported the enantioselective synthesis of functionalized cyclopentanone oximes bearing three stereogenic centers in good yields of up to 84%, complete diastereoselectivity, and high enantioselectivities of up to 98% ee on the basis of a cascade reaction occurring between 2-allylmalonates and nitroalkenes catalyzed by cinchona alkaloid **4** (Figure 37.1) [24]. On the other hand, triflate salts of camphor-derived cyclic hydrazides **5a**,**b** (Figure 37.1) have been demonstrated by Ogilvie *et al.* to be efficient organocatalysts in inducing chirality in the [3+2] cycloaddition of nitrones with enals [25]. This novel system nicely complemented other examples of organocatalyzed cycloadditions, since it allowed access to the *exo*-cycloadducts in contrast with other methods, which often favored the *endo*-cycloadducts. Despite moderate diastereoselectivities (≤36% de), the *exo*- and *endo*-cycloadducts were obtained with enantioselectivities of up to 93 and 94% ee, respectively. Chiral BINOL-derived phosphoramides (BINOL = 1,1′-bi-2-naphthol), such as **6** (Figure 37.1), were employed by Yamamoto *et al.* in the 1,3-dipolar cycloaddition of nitrones and ethyl vinyl ether [26]. Only 5 mol% of this air-stable catalyst was needed to lead completion of the reaction in 1 h, yielding the corresponding *endo*-cycloadducts as major diastereomers with high diastereoselectivities of up to 94% de and excellent yields, combined with high enantioselectivities of up to 93% ee. In addition, Jurczak *et al.* have introduced the use of (*S*)-BINAM-diamides (BINAM = 1,1′-binaphthalenyl-2,2′-diamine) to promote the [3+2] cycloaddition of aromatic nitrones to (*E*)-crotonaldehyde [27]. The best results were obtained by using L-phenylalanine-based catalyst **7** (Figure 37.1), affording the corresponding cycloadducts with *endo*-diastereoselectivities of up to 76% de and enantioselectivities of up to 95% ee. Furthermore, this type of catalyst was applied to develop the first organocatalytic enantioselective reaction of alkyl glyoxylate-derived nitrones with (*E*)-crotonaldehyde [28]. In this case, a catalyst loading as low as 5 mol% was effective in promoting the reaction, furnishing the corresponding isoxazolidinones in good yields (up to 95%) and diastereoselectivities (≤84% de) as well as enantioselectivities of up to 91% ee.

37.2.1.2 **[3+2] Cycloadditions of Azomethine Ylides**

The use of azomethine ylides in organocatalysis has recently received much attention. Azomethine ylides are planar 1,3-dipoles composed of a central nitrogen atom and two terminal sp^2 carbon atoms. Their cycloaddition to olefinic dipolarophiles provides a direct and general method for the synthesis of pyrrolidine derivatives. Normally, the azomethine ylides are generated *in situ* and trapped by a multiple C–C or C–X bond. The first organocatalytic 1,3-dipolar cycloaddition of azomethine ylides was reported by Arai *et al.*, in 2006 [29]. In this work, a D_2-symmetrical ammonium salt as a phase-transfer catalyst was employed to promote the reaction between *t*-butyl alaninate and methyl acrylate, providing the corresponding cycloadduct in low yield and enantioselectivity. The first highly enantioselective organocatalytic 1,3-dipolar cycloaddition with azomethine ylides was described in 2007 by Vicario *et al.* [30]. As shown in Scheme 37.2, the reaction of azomethine ylides generated from arylideneiminomalonates **14** with enals, catalyzed by (*S*)-α,α-diphenylprolinol **15** and performed without the presence of a base, afforded diastereoselectively the corresponding *endo*-highly functionalized polysubstituted pyrrolidines **16** with high yields (74–91%) and enantioselectivities (85 to >99% ee).



R^1 = Ph, R^2 = Me: 89% *endo:exo* >95:5 ee = 98%
R^1 = Ph, R^2 = Et: 91% *endo:exo* >95:5 ee = 97%
R^1 = Ph, R^2 = *n*-Bu: 88% *endo:exo* >95:5 ee = 99%
R^1 = R^2 = Ph: 82% *endo:exo* >95:5 ee >99%
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$: 91% *endo:exo* = 92:8 ee >99%
R^1 = Ph, R^2 = 2-Fu: 90% *endo:exo* >95:5 ee = 98%
R^1 = *p*-FC_6H_4, R^2 = Me: 74% *endo:exo* >95:5 ee = 98%
R^1 = *o*-Tol, R^2 = Me: 91% *endo:exo* >95:5 ee = 99%
R^1 = 2-Fu, R^2 = Me: 84% *endo:exo* >95:5 ee = 98%

Scheme 37.2 Synthesis of pyrrolidines through [3+2] cycloaddition of arylidene-iminomalonates and enals.

Cinchona alkaloid thiourea catalyst **17** (Figure 37.2) was later employed by Gong *et al.* to induce the enantio- and diastereoselective 1,3-dipolar cycloaddition of azomethine ylides generated from Schiff bases and nitroalkenes [31]. This process provided straightforward access to chiral highly substituted pyrrolidines with good yields, moderate enantioselectivities (≤63% ee), and excellent diastereoselectivities of up to 98% de. Higher enantioselectivities of up to 92% ee were reported by Takemoto *et al.* for the [3+2] cycloaddition of azomethine ylides generated from ethyl 2-(arylideneimino)malonates and nitroalkenes by using another thiourea catalyst (**18**, Figure 37.2) [32]. The corresponding functionalized pyrrolidines were obtained with high diastereo- and enantioselectivities of up to 92% ee combined with good to high yields (72–86%). On the other hand, an efficient kinetic resolution of 3-nitro-2*H*-chromenes catalyzed by the same catalyst yielded the recovered enantioenriched (*R*)-3-nitro-2*H*-chromene derivatives with moderate to good enantioselectivities (≤87% ee), along with the corresponding 1,3-dipolar cycloadducts, diethyl 3,4-diphenyl-3α-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate derivatives bearing four vicinal chiral carbon centers with moderate enantioselectivities (≤70% ee) [33]. In addition, catalyst **19** (Figure 37.2) was employed to promote the intramolecular [3+2] cycloaddition of ethyl 4-(2-formylphenoxy)butenoate with amino esters, providing the corresponding hexahydrochromeno[4,3-*b*] pyrrolidine derivatives in high diastereo- and enantioselectivities of up to 98% de and 94% ee, respectively [34]. On the other hand, Terada and Nakano have developed the [3+2] cycloaddition of dialkyl maleates, such as dimethyl maleate, with azomethine ylides generated from Schiff bases by using chiral guanidine **20** (Figure 37.2) as catalyst, which led to the corresponding pyrrolidines with a high *endo*-diastereoselectivity of >97% de [35]. Despite a remarkable low catalyst loading of 2 mol%, these cycloadducts were isolated in moderate to high yields (21–90%) and enantioselectivities (59–91% ee). In addition, α-amino acids, such as chiral proline, 3- and 4-hydroxyprolines, glutamic acid, and tryptophan, among others, have been investigated by Kudryavtsev and Zagulyaeva as catalysts in the [3+2] cycloaddition of iminoesters with maleimides, fumarates, and maleic anhydride, giving low enantioselectivities (≤12% ee) [36]. Azomethine imines have also been

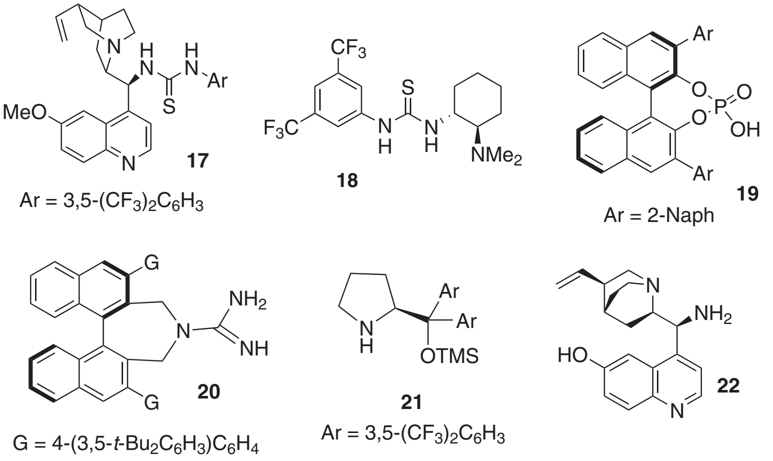


Figure 37.2 Organocatalysts used in [3+2] cycloadditions of azomethine ylides (TMS = trimethylsilyl).

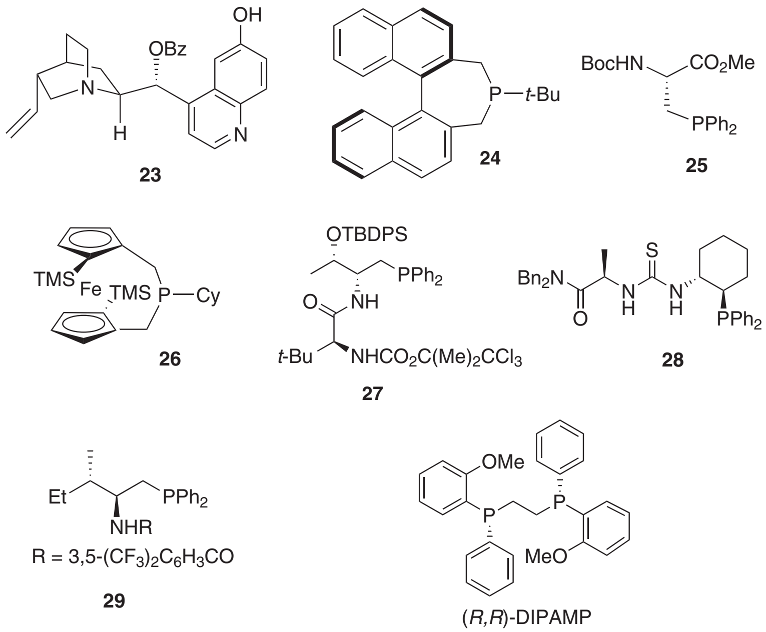
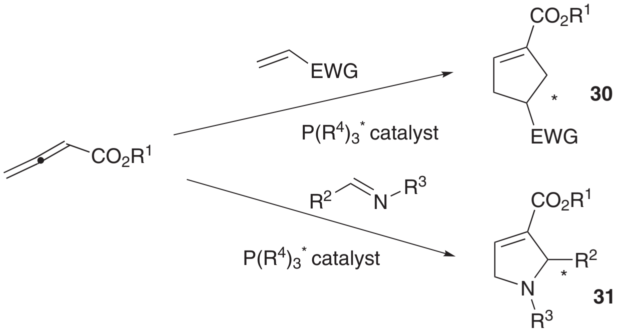


Figure 37.3 Organocatalysts used in [3+2] cycloadditions of phosphonium-inner salts (Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Cy = cyclohexyl, TBDPS = *tert*-butyldiphenylsilyl).

used in organocatalytic 1,3-dipolar cycloaddition with renowned success. For example, Chen *et al.* developed, in 2006, a very elegant 1,3-dipolar cycloaddition between aliphatic enals and azomethine imines [37]. The reaction was efficiently catalyzed by Jorgensen's catalyst **21** (Figure 37.2), affording the corresponding cycloadducts in good yields (40–95%) and enantioselectivities (77–96% ee), albeit with moderate diastereoselectivities (62–90% de), with the *exo*-adduct as the major diastereomer. In 2007, these authors reported the 1,3-dipolar cycloaddition of azomethine imines with cyclic enones instead of enals promoted by multifunctional primary amines derived from cinchona alkaloids, such as **22** (Figure 37.2), which provided the corresponding cycloadducts in good yields (76–90%) and high enantioselectivities (90–93% ee) [38]. More recently, Suga *et al.* have developed 1,3-dipolar cycloadditions of cyclic azomethine imines with acrolein catalyzed by L-proline and its derivatives [39]. In particular, the reactions catalyzed by (*S*)-indoline-2-carboxylic acid afforded the corresponding *exo*-cycloadducts with high diastereoselectivities in the range 82–98% de and good to excellent enantioselectivities ranging from 75 to 98% ee.

37.2.1.3 **Miscellaneous [3+2] Cycloadditions**

The first catalytic asymmetric 1,3-dipolar cycloaddition of α-substituted isocyanoesters and nitroolefins was reported by Gong *et al.*, in 2008 [40]. This process was based on the use of cinchona alkaloid derivatives, such as **23** (Figure 37.3), as organocatalysts to afford the corresponding chiral 2,3-dihydropyrroles with high diastereo- and enantioselectivities of up to >90% de and >99% ee, respectively. In another context, a series of elegant [3+2] cycloadditions of allenoates and electron-deficient alkenes or imines catalyzed by tertiary chiral phosphanes has been successfully developed in recent years. First reported by Lu and Zhang in 1995, this methodology is one of the most powerful methods for obtaining functionalized cyclopentenes [41]. These reactions are normally triggered by phosphane attack to the β-carbon of the alkyl allenoate generating an 1,3-dipole, which is an inner salt containing a phosphonium cation. This zwitterionic species subsequently undergoes a 1,3-dipolar cycloaddition with an electrophilic alkene, affording enantiomerically enriched carbocycle **30** (Scheme 37.3). These reactions were also induced by chiral phosphabicyclo[2.2.1]heptanes as catalysts by Zhang *et al.*, in 1997 [42]. In addition, if an imine is employed as dipolarophile, a chiral Δ^3-pyrrolidine (**31**) is formed. (Scheme 37.3).



Scheme 37.3 Synthesis of five-membered compounds through [3+2] cycloadditions of allenoates and electron-deficient alkenes or imines catalyzed by tertiary phosphane (EWG = electron-withdrawing group).

In 2006, Fu *et al.* developed a new phosphine catalyst (**24**, Figure 37.3) derived from BINOL, which was successfully employed in [3+2] cycloadditions between allenoates and a wide range of enones, affording polysubstituted cyclopentenes in moderate to good yields (39–74%) and enantioselectivities (69–90% ee) [43]. Later, Miller and Cowen developed the [3+2] cycloaddition of benzyl allenoate with bicyclic enones catalyzed by chiral (diphenylphosphino)methylglycine derivative **25** (Figure 37.3), which provided the corresponding α-cycloadducts as major products in good yields (53–95%) and enantioselectivities (65–84% ee) [44]. The scope of the reaction was extended to the reaction of γ-methyl-substituted benzyl allenoate with a series of simple acyclic enones with both high yields (of up to 96%) and enantioselectivities (87–93% ee). Similar reactions catalyzed by chiral DIOP [2,3-(isopropylidenedioxy)-2,3-dihydroxy-l,4-bis(diphenylphosphanyl)butane] were developed by Wallace *et al.*, giving enantioselectivities of ≤77% ee [45]. On the other hand, Marinetti *et al*. have demonstrated that the use of chiral ferrocenyl phosphane **26** (Figure 37.3) as catalyst in the [3+2] cycloaddition of ethyl allenoate with a range of both cyclic and acyclic enones affords the corresponding γ-cycloadducts as major regioisomers in good yields of up to 87% combined with high enantioselectivities (84–96% ee) [46]. A similar methodology was applied by Krische *et al*. to the synthesis of the natural product (+)-geniposide [47]. In 2010, Marinetti *et al*. extended the scope of this methodology to a set of acyclic and cyclic dienones, which afforded the corresponding cyclopentenes with good yields, and both high regio- and enantioselectivities (≤93% ee) [48]. In addition, this catalyst has been shown to be the first efficient organocatalyst for the enantioselective synthesis of cyclopentenylphosphonates through [3+2] cycloaddition between diethyl allenylphosphonate and enones [48, 49]. While allenoates have been widely used in this type of cycloaddition, the corresponding allenones have been much less studied since they can afford competitive self-dimerized [4+2] cycloadducts. In this context, Loh and Sampath have demonstrated that the use of α-trimethylsilyl-substituted aromatic allenones solved this problem due to the steric bulk of the silicon, thus affording the desired cross-[3+2] cycloadducts [50]. Thus, a highly regioselective synthesis of chiral functionalized cyclopentenes was achieved through [3+2] cycloaddition of α-trimethylsilyl-substituted aromatic allenones with electron-deficient olefins. Indeed, this process provided regioselectively a series of [3+2] γ-cycloadducts in moderate to good yields and enantioselectivities of up to 92% ee, when catalyzed by a chiral diphosphine, such as (*S,S*)-Et-DUPHOS [DUPHOS = 1,2-bis(phospholano)benzene]. Very recently, Lu *et al*. introduced a new family of dipeptide-based chiral phosphines as catalysts to be applied to the α-regioselective [3+2] cycloaddition of *t*-butyl allenoate and α-substituted acrylates [51]. For example, the use of D-Thr-L-*tert*-Leu-derived catalyst **27** (Figure 37.3) allowed a range of functionalized cyclopentenes as the sole α-regioisomers to be obtained in both excellent yields and enantioselectivities of up to 94% ee. *N*-Tosyl arylimines and *N*-diphenylphosphinoyl imines were used as dipolarophiles in the [3+2] cycloaddition of allenoates by Marinetti *et al*., yielding the corresponding α-cycloadducts in moderate to good enantioselection (≤92% ee) [52]. A new class of chiral bifunctional thiourea catalysts derived from *trans*-2-amino-1-(diphenylphosphino)cyclohexane, such as **28** (Figure 37.3), was developed by Jacobsen and Fang to be applied to the reaction of ethyl allenoate with *N*-diphenylphosphinoyl imines, which provided cycloadducts in excellent enantioselectivities of up to 98% ee [53]. On the other hand, highly regio- and enantioselective [3+2] cycloadditions between ethyl allenoate and arylidene-malononitriles and analogues have been recently developed by Zhao *et al*. by using novel bifunctional *N*-acyl-aminophosphine catalysts derived from α-amino acids, such as **29** (Figure 37.3), which furnished the corresponding cycloadducts in high yields and high enantioselectivities (80–99% ee) [54]. This type of reaction was also developed by Marinetti *et al*., who obtained comparable results in terms of yields and enantioselectivities [55]. A problem associated with the preceding processes based on the use of allenoates is the difficulty encountered in their preparation. Furthermore, these compounds are sometimes contaminated with the corresponding homo-propargylic equivalents. In this sense, the use of 3-butynoates, which can be isomerized to the corresponding allenoates *in situ*, for the [3+2] cycloaddition with electron-deficient enones was interesting. In this context, Loh and Sampath have demonstrated the direct applicability of 3-butynoates in this type of cycloaddition by achieving highly enantio-, regio- and diastereoselective one-pot [3+2] cycloadditions catalyzed by (*R,R*)-DIPAMP {ethane-1,2-diylbis[(2-methoxyphenyl) phenylphosphane]} (Figure 37.3) via isomerization of 3-butynoates into the corresponding allenoates [56]. Indeed, the reaction of variously substituted 3-butynoates with a range of enones led to the corresponding cycloadducts as single regio- and diastereomers with both excellent yields and enantioselectivities of up to 99% ee.

37.2.2
Five-Membered Cycles via Domino Reactions

Since the first organocatalytic asymmetric domino reaction reported by Bui and Barbas in 2000 [57], an tremendous number of these powerful and fascinating processes have been developed, which have allowed complex chiral molecular architectures to be built from simple materials with high yields and very often remarkable enantioselectivities in a metal-free environment [58]. Indeed, the possibility of joining two or more organocatalytic reactions in one asymmetric domino process has become a challenging goal for chemists [59], due to several advantages from an economical and environmental point of view, avoiding, for example, costly protecting groups and time-consuming purification procedures after each step.

37.2.2.1 Domino Reactions Initiated by the Michael Reaction

37.2.2.1.1 Domino Michael–Michael Reactions

Michael-type reactions can be considered as one of the most powerful and reliable tools for the stereocontrolled formation of carbon–carbon and carbon–heteroatom bonds [60]. As a consequence, in recent years, many different organocatalytic versions of this important transformation have been integrated in domino reactions [61]. Among them, domino Michael–Michael reactions have allowed highly functionalized chiral five-membered carbocycles to be obtained. For example, Wang *et al.* have developed such reactions initiated by a carbo-conjugated addition of malonate derivatives, such as γ-malonate-α,β-unsaturated esters, to enals catalyzed by amine **8**, providing the corresponding cyclopentanes in high yields (87–92%) and high diastereo- (80–90% de) and enantioselectivities (84–99% ee) [62]. Later, Zhong *et al.* developed asymmetric domino Michael–Michael reactions between nitrostyrenes and diethyl 5-acetylhex-2-enedionate catalyzed by cinchona alkaloid derivatives such as **32** (Figure 37.4) [63]. This process consisted of the keto ester Michael addition to a nitrostyrene and subsequent intramolecular cyclization via a Michael addition of the nitro compound and α,β-unsaturated ester. The reaction was possible due to the low reactivity as Michael acceptors of unsaturated esters in comparison with nitrostyrenes. It furnished the corresponding tetrasubstituted cyclopentanes with good yields (87–91%) and in almost diastereo- (90–98% de)

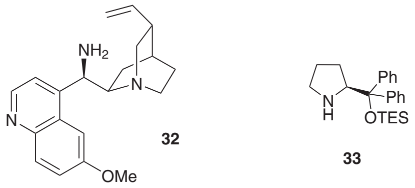


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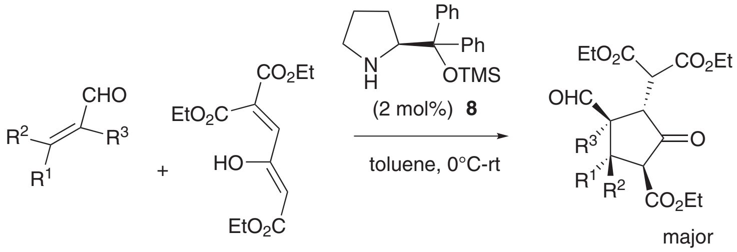
Figure 37.4 Organocatalysts used in domino Michael–Michael reactions (TES = triethylsilyl).

and enantiopure form (95–97% ee). This type of reaction has also been developed by Cordova *et al.* upon catalysis with (*S*)-diphenylprolinol triethylsilyl ether **33** by using γ-nitro-α,β-unsaturated esters as nucleophiles, providing the corresponding cyclopentanes in excellent enantioselectivities of up to 99% ee, albeit with lower diastereoselectivities [64].

In 2010, amine **8** was employed by Ma *et al.* to promote an enantioselective synthesis of polysubstituted cyclopentanones **34** through domino Michael–Michael reactions of a range of enals with keto ester **35** bearing a highly electron-deficient olefin unit (Scheme 37.4) [65]. This process allowed the formation of four contiguous stereocenters in the cyclopentanone ring with excellent enantioselectivities of up to >99% ee through an iminium–enamine activation mode. The scope of the process was extended to various β-, α,β-, and β,β-substituted α,β-unsaturated aldehydes, including cyclic enals, providing excellent enantioselectivities and moderate to high diastereoselectivities (22–92% de). Notably, compared with many Michael additions of enals catalyzed by secondary amines this novel double Michael addition process required less catalyst (2 mol%).



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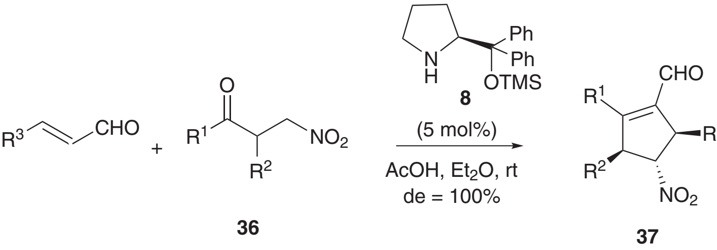
R^1 = *p*-MeOC_6H_4, R^2 = H, R^3 = H: 79% de = 92% ee >99%
R^1 = *p*-FC_6H_4, R^2 = H, R^3 = H: 83% de = 88% ee = 99%
R^1 = *p*-MeOC_6H_4, R^2 = H, R^3 = H: 95% de = 88% ee >99%
R^1 = 2-Fu, R^2 = H, R^3 = H: 89% de = 88% ee = 98%
R^1 = Me, R^2 = H, R^3 = H: 86% de = 90% ee = 95%
R^1 = (*Z*)-*n*-Pr-CH=CH-Me, R^2 = H, R^3 = H: 70% de = 92% ee = 98%
R^1 = R^3 = Me, R^2 = H: 70% de = 92% ee = 90%
R^1 = Ph, R^2 = H, R^3 = Me: 67% de = 82% ee = 95%
R^1 = R^2 = Me, R^3 = H: 90% de = 42% ee >99%
R^1 = Ph, R^2 = Me, R^3 = H: 82% de = 22% ee >99%
R^1 = H, R^2, R^3 = $(CH_2)_5$: 90% de = 58% ee >99%

Scheme 37.4 Synthesis of cyclopentanones through a domino Michael–Michael reaction.

In marked contrast with the Michael addition of carbon nucleophiles, the addition of non-carbon nucleophiles (hetero-Michael addition) has received considerably less interest in past decades. A very recent example of an asymmetric domino thia-Michael–Michael reaction was described by Wang *et al.* by using chiral bifunctional thiourea **18** (Figure 37.2) as catalyst [66]. This novel hydrogen-bonding-mediated highly stereoselective reaction of *trans*-ethyl-4-sulfanyl-2-butenoate with (*E*)-β-nitrostyrenes led to the corresponding biologically significant trisubstituted tetrahydrothiophenes bearing three stereogenic centers with high enantio- and diastereoselectivities of up to 97% ee and >94% de, respectively.

37.2.2.1.2 **Domino Michael–Aldol Reactions**

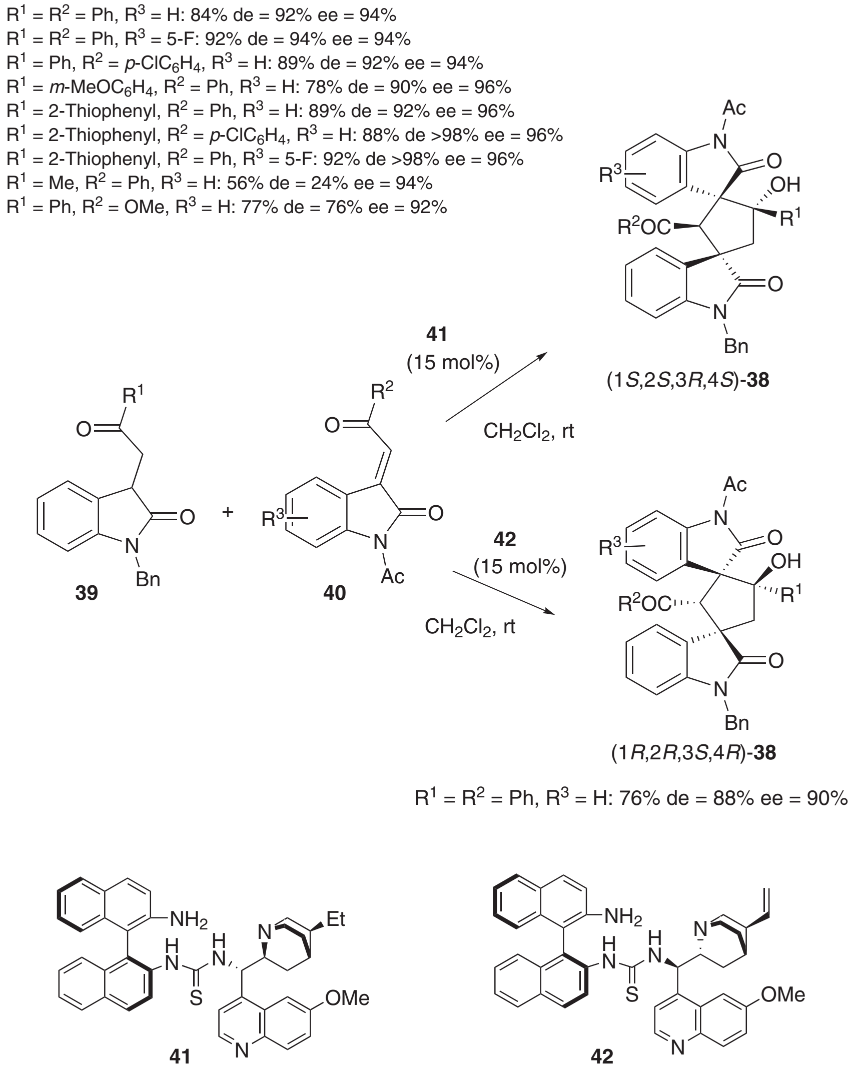
Since the early example of a proline-catalyzed asymmetric domino Michael–aldol reaction reported by Bui and Barbas in 2000 [57], a number of these reactions have been successfully developed by several groups. For example, Wang *et al.* have reported the synthesis of chiral densely functionalized cyclopentenes on the basis of a domino Michael–aldol reaction followed by dehydration between aromatic enals and dimethyl 2-oxoethylmalonate [67]. High yields (63–89%) and enantioselectivities (91–97% ee) were obtained by using (*S*)-diphenylprolinol silyl ethers as catalysts. On the other hand, the condensation of β-nitroketones **36** onto enals in the presence of **8** was shown by Hong *et al.* to afford the corresponding domino Michael–aldol products **37** through the iminium–enamine activation mode [68]. The formed fully substituted cyclopentene derivatives were obtained as single diastereomers in moderate to good yields and excellent enantioselectivities of up to 99% ee (Scheme 37.5).



R^1	R^2	R^3	Yield (%)	ee (%)
p-BrC$_6$H$_4$	*n*-Pr	*p*-MeOC$_6$H$_4$	54	>99
p-BrC$_6$H$_4$	*n*-Pr	3,4-MeO$_2$C$_6$H$_3$	60	97
p-BrC$_6$H$_4$	*n*-Pr	3-OMe-4-OAcC$_6$H$_3$	63	98
p-BrC$_6$H$_4$	*n*-Hex	*p*-MeOC$_6$H$_4$	55	99
p-BrC$_6$H$_4$	*n*-Pr	*m*-NO$_2$C$_6$H$_4$	48	>99
p-BrC$_6$H$_4$	*n*-Pr	*p*-NMe$_2$C$_6$H$_4$	58	92
p-ClC$_6$H$_4$	*n*-Hex	3-OMe-4-OEtC$_6$H$_3$	68	96

Scheme 37.5 Synthesis of cyclopentenes through a domino Michael–aldol reaction (Hex = cyclohexyl).

The iminium–enamine activation mode was also applied by Rueping *et al.* to the domino Michael–aldol reaction of enals with 1,2-cyclohexadione, which provided access upon catalysis with amine **8** to the corresponding chiral bicyclo[3.2.1] octane-6-carbaldehydes as single diastereomers in good yields and with excellent enantioselectivities (90–98% ee) [69]. Asymmetric domino hetero-Michael–aldol reactions affording five-membered cycles have also been developed quite recently by several other groups [70]. As a recent example, Vicario *et al.* have developed domino oxa-Michael–aldol-hemiacetalization reactions of enals with dihydroxyacetone dimer, which led upon catalysis with **8** to the enantioselective formation of the corresponding hexahydrofuro[3, 4-c]furans bearing four stereocenters in high enantioselectivities (90–99% ee) in combination with good diastereoselectivity (>82% de) [71]. The iminium–enamine activation mode has also been applied by Enders *et al.* to enantioselective domino aza-Michael–aldol reactions catalyzed by **8** [72]. These novel processes opened efficient and enantioselective entry to the tricyclic pyrrolo-indole core, which is a characteristic structural unit of many bioactive natural products. In the same context, a series of chiral 3-substituted 3*H*-pyrrolo[1,2-*a*]indoles were obtained in moderate to good yields (40–71%) and high to excellent enantioselectivities (85 to >99% ee) by reaction of 1*H*-indole-2-carbaldehyde and enals. In 2010, Wang *et al.* reported the same reaction, only changing the solvent, using toluene instead of MTBE (methyl *tert*-butyl ether) [73]. Furthermore, several groups have successfully developed the synthesis of chiral five-membered cycles through asymmetric domino thia-Michael–aldol reactions based on the iminium–enamine activation mode. For example, Wang *et al.* have used the closely related diarylprolinol silylether **21** (Figure 37.2) to promote the synthesis of chiral highly functionalized tetrahydrothiophenes by reaction of enals with ethyl-sulfanyl-2-oxopropanoate [74]. Notably, three consecutive stereogenic centers, including one chiral quaternary carbon center, were efficiently created in this process with moderate to good yields associated with high enantioselectivities (91–97% ee) and diastereoselectivities (78 to >90% de). In the same context, Xu *et al.* have condensed 2-sulfanylacetaldehyde, generated from 1,4-dithiane-2,5-diol under equilibrium conditions, with enals in the presence of catalyst **8**, providing the corresponding domino five-membered thia-Michael–aldol products in high yields and excellent enantioselectivities of up to >99% ee [75]. The hydrogen-bonding activation mode was very recently invoked by Barbas *et al.* to explain the formation of chiral complex bi-spirooxindoles (1*S*,2*S*,3*R*,4*S*)-**38** on the basis of a novel asymmetric domino Michael–aldol reaction occurring between 3-substituted oxindoles **39** and a range of methylene-indolinones **40** [76]. This process was catalyzed by the novel multifunctional organocatalyst **41**, containing tertiary and primary amines and thiourea moieties, to activate substrates simultaneously, providing extraordinary levels of stereocontrol over four stereocenters, three of which were quaternary carbon centers. As shown in Scheme 37.6, this novel methodology provided facile access to several potent biologically active multisubstituted bi-spirocyclooxindole derivatives **38** with high yields and excellent diastereo- and enantioselectivities of up to >98% de and 96% ee, respectively. Even more interestingly, these authors have proposed the possibility of obtaining the opposite


$R^1 = R^2 = Ph, R^3 = H$: 84% de = 92% ee = 94%
$R^1 = R^2 = Ph, R^3 = 5\text{-F}$: 92% de = 94% ee = 94%
$R^1 = Ph, R^2 = p\text{-ClC}_6H_4, R^3 = H$: 89% de = 92% ee = 94%
$R^1 = m\text{-MeOC}_6H_4, R^2 = Ph, R^3 = H$: 78% de = 90% ee = 96%
R^1 = 2-Thiophenyl, $R^2 = Ph, R^3 = H$: 89% de = 92% ee = 96%
R^1 = 2-Thiophenyl, $R^2 = p\text{-ClC}_6H_4, R^3 = H$: 88% de >98% ee = 96%
R^1 = 2-Thiophenyl, $R^2 = Ph, R^3 = 5\text{-F}$: 92% de >98% ee = 96%
$R^1 = Me, R^2 = Ph, R^3 = H$: 56% de = 24% ee = 94%
$R^1 = Ph, R^2 = OMe, R^3 = H$: 77% de = 76% ee = 92%

$R^1 = R^2 = Ph, R^3 = H$: 76% de = 88% ee = 90%

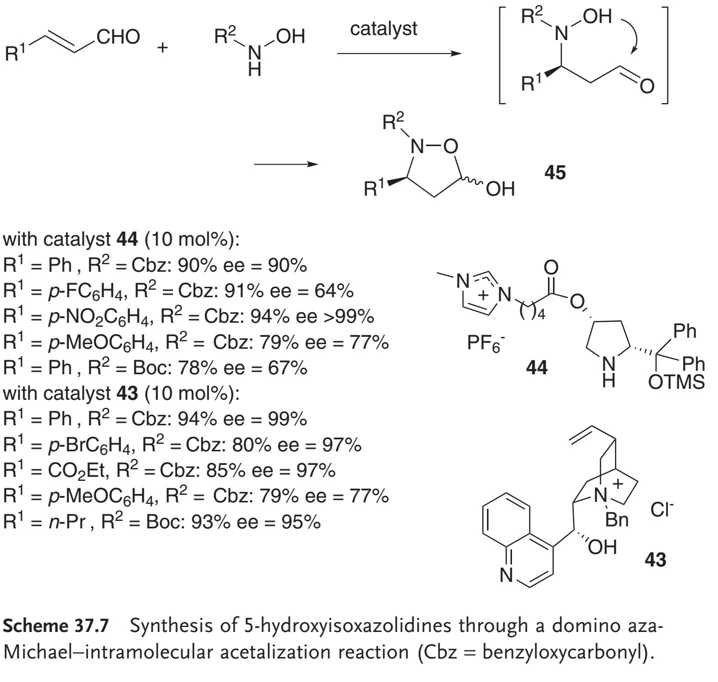
Scheme 37.6 Synthesis of bispirocyclooxindoles through a domino Michael–aldol reaction.

enantiomers (1*R*,2*R*,3*S*,4*R*)-**38** by performing the reaction in the presence of a reconfigured catalyst **42**, in which the (*S*)-diamine component was kept and the tertiary amine and the thiourea configurations were changed compared with catalyst **41**.

37.2.2.1.3 **Domino Michael–Intramolecular Heterocyclization Reactions**

One common strategy for the synthesis of oxa- or aza-five-membered cycles consists of first a Michael addition to an activated alkene followed by hemi-acetal or

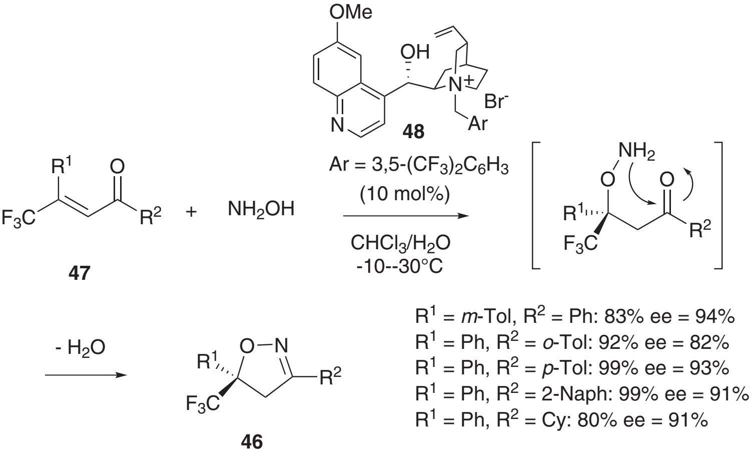
-aminal formation that furnishes the final heterocycle. An early example of asymmetric domino Michael–hemiaminal formation reactions was reported by Rios *et al.*, in 2007 [77]. The reaction of 2-aminomalonates with aromatic enals catalyzed by amine **8** furnished the corresponding chiral pyrrolidines with good yields (71–76%), moderate to good diastereoselectivities (66–82% de), and high enantioselectivities (90–99% ee). A related reaction was later developed by Franzen *et al.*, leading to chiral quinazolidines by the reaction of malonic acid monoamide derivatives with enals [78]. This domino reaction was efficiently induced by the same catalyst, affording the desired indolo[2,3-*a*]quinolizidines and benzo[*a*]quinolizidines with good yields (56–71%) and high enantioselectivities (87–98% ee), albeit with moderate diastereoselectivities (24–70% de). In 2007, Cordova *et al.* developed an elegant synthesis of 5-hydroxyisoxazolidine compounds based on the addition of *N*-protected hydroxyamines to enals involving aza-Michael addition and intramolecular acetalization steps upon catalysis with cinchona alkaloid-derived phase-transfer catalyst **43** [79]. The products were obtained in excellent enantioselectivities of up to 99% ee and high yields (80–95%) and could be easily converted into chiral β-amino acids. Later, Zlotin *et al.* demonstrated that these reactions could also be performed upon catalysis with chiral ionic liquid **44** bearing an α,α-diphenylprolinol unit [80]. Indeed, a set of 5-hydroxy-3-arylisoxazolidines **45** were achieved in excellent yields and with moderate to high enantioselectivities (64 to >99% ee) (Scheme 37.7).



with catalyst **44** (10 mol%):
R^1 = Ph , R^2 = Cbz: 90% ee = 90%
R^1 = p-FC_6H_4, R^2 = Cbz: 91% ee = 64%
R^1 = p-$NO_2C_6H_4$, R^2 = Cbz: 94% ee >99%
R^1 = p-$MeOC_6H_4$, R^2 = Cbz: 79% ee = 77%
R^1 = Ph , R^2 = Boc: 78% ee = 67%
with catalyst **43** (10 mol%):
R^1 = Ph , R^2 = Cbz: 94% ee = 99%
R^1 = p-BrC_6H_4, R^2 = Cbz: 80% ee = 97%
R^1 = CO_2Et, R^2 = Cbz: 85% ee = 97%
R^1 = p-$MeOC_6H_4$, R^2 = Cbz: 79% ee = 77%
R^1 = n-Pr , R^2 = Boc: 93% ee = 95%

Scheme 37.7 Synthesis of 5-hydroxyisoxazolidines through a domino aza-Michael–intramolecular acetalization reaction (Cbz = benzyloxycarbonyl).

Since heterocycles containing a trifluoromethyl group are representatives of a major structure type in agricultural and medicinal chemistry, Shibata *et al.* have developed a novel enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines **46** on the basis of a domino oxa-Michael–intramolecular hemi-aminalization–dehydration reaction of hydroxylamine with a range of (*E*)-trifluoromethylated enone derivatives **47** [81]. This process, which employed *N*-3,5-bis(trifluoromethyl)benzyl-quinidinium bromide **48** as a chiral phase-transfer catalyst combined with CsOH as a base provided a series of trifluoromethyl-substituted 2-isoxazolines **46** in high yields and enantioselectivities of up to 94% ee (Scheme 37.8).

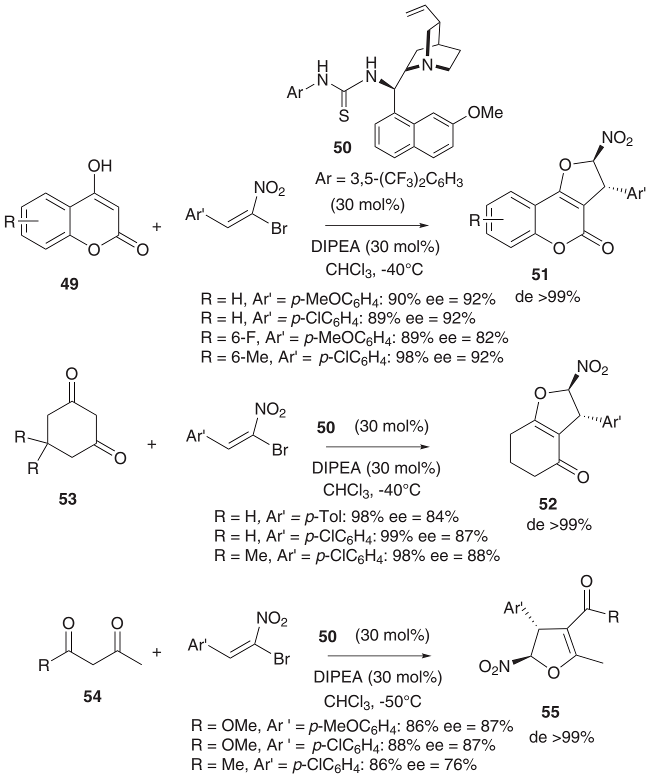


R^1 = *m*-Tol, R^2 = Ph: 83% ee = 94%
R^1 = Ph, R^2 = *o*-Tol: 92% ee = 82%
R^1 = Ph, R^2 = *p*-Tol: 99% ee = 93%
R^1 = Ph, R^2 = 2-Naph: 99% ee = 91%
R^1 = Ph, R^2 = Cy: 80% ee = 91%

Scheme 37.8 Synthesis of trifluoromethyl-substituted 2-isoxazolines through a domino oxa-Michael–intramolecular hemi-aminalization–dehydration reaction.

37.2.2.1.4 **Domino Michael–Intramolecular AlkylationReactions**

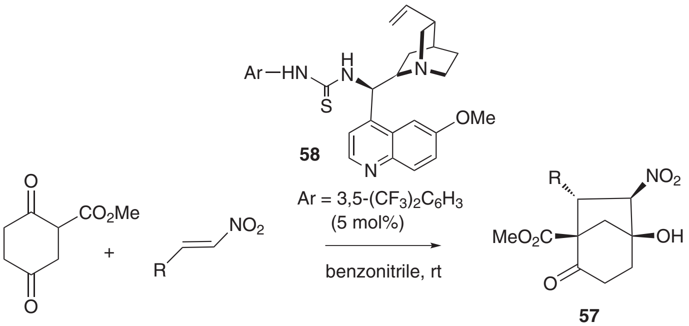
Several groups have developed asymmetric domino reactions involving a Michael addition followed by an intramolecular alkylation for the synthesis of chiral functionalized cyclopropanes (Section 37.4) [82]. Employing a domino Michael–alkylation reaction similar to that reported in their cyclopropanation [82b], Cordova *et al.* developed later an enantioselective synthesis of cyclopentanones starting from enals and 4-bromo-acetoacetate under the effect of catalyst **8** in the presence of one equivalent of potassium carbonate [83]. The formed cyclopentanones bearing three stereogenic centers were obtained in good to high yields (70–83%), moderate diastereoselectivities (72–84% de), and high enantioselectivities (93–99% ee). Soon after this, Enders *et al.* reported a powerful domino reaction between aliphatic aldehydes and 5-iodonitroalkenes catalyzed by the same catalyst [84]. The aldehyde reacted with the catalyst to generate the corresponding enamine, which underwent a Michael addition to the nitroalkene. The intermediate enamine reacted via an intramolecular alkylation to afford the desired cyclopentanes in good yields (59–62%), moderate diastereoselectivities (32–74% de), and excellent enantioselectivities (94–97% ee). Another asymmetric domino Michael–alkylation methodology has been independently developed by Xie *et al.* [85] and Rueping *et al.* [86] for the enantioselective synthesis of a range of chiral 2,3-dihydrofurans from the reaction of α-bromonitroalkenes with 1,3-dicarbonyl compounds. In both cases, the catalysts were chiral bifunctional thioureas associated with a base, such as DIPEA (diisopropylethylamine) or TMEDA (tetramethylethylenediamine). For example, the reaction of bicyclic 1,3-dicarbonyl compounds, such as 4-hydroxyl(thio)coumarins **49**, led in the presence of catalyst **50** to the corresponding tricyclic 2,3-dihydrofurans **51** in high yields of up to 98%, excellent diastereoselectivities of up to >99% de, and high enantioselectivities (82–92% ee). The scope of this process was extended to the synthesis of chiral bicyclic 2,3-dihydrofurans **52** by the reaction of α-bromonitroalkenes with cyclohexane-1,3-diones **53**, which provided comparable diastereoselectivities (>99% de) combined with general excellent yields (96–99%) and high enantioselectivities of up to 88% ee (Scheme 37.9). The scope of this domino reaction was further extended to acyclic 1,3-dicarbonyl compounds **54**, which afforded the corresponding chiral monocyclic 2,3-dihydrofurans **55** in comparable diastereoselectivities (>99% de), high yields (86–88%), and good enantioselectivities (76–87% ee) (Scheme 37.9).


50
Ar = 3,5-(CF3)2C6H3
(30 mol%)
DIPEA (30 mol%)
CHCl3, -40°C
49
51
de >99%
R = H, Ar' = p-MeOC6H4: 90% ee = 92%
R = H, Ar' = p-ClC6H4: 89% ee = 92%
R = 6-F, Ar' = p-MeOC6H4: 89% ee = 82%
R = 6-Me, Ar' = p-ClC6H4: 98% ee = 92%
50 (30 mol%)
DIPEA (30 mol%)
CHCl3, -40°C
53
52
de >99%
R = H, Ar' = p-Tol: 98% ee = 84%
R = H, Ar' = p-ClC6H4: 99% ee = 87%
R = Me, Ar' = p-ClC6H4: 98% ee = 88%
50 (30 mol%)
DIPEA (30 mol%)
CHCl3, -50°C
54
55
de >99%
R = OMe, Ar ' = p-MeOC6H4: 86% ee = 87%
R = OMe, Ar ' = p-ClC6H4: 88% ee = 87%
R = Me, Ar' = p-ClC6H4: 86% ee = 76%

Scheme 37.9 Synthesis of mono-, bi-, and tricyclic 2,3-dihydrofurans through domino Michael–alkylation reactions.

37.2.2.1.5 Domino Michael–(aza)-Henry Reactions

The Henry reaction has been associated recently with the Michael addition in successful asymmetric domino sequences [87]. For example, Zhong *et al.* have reported an asymmetric domino Michael–Henry reaction promoted by cinchona alkaloid derivative **32**, which provided chiral cyclopentanes in excellent yields (91–93%) and in almost diastereo- and enantiopure form (92–95% ee) starting from nitroalkenes and 1,3-dicarbonyl compounds [88]. In 2010, Zhao *et al.* [89], and Rueping *et al.* [90] independently developed comparable reactions induced by chiral bifunctional cinchona thioureas, providing a range of chiral synthetically unique and medicinally important bicyclo[3.2.1]octan-8-ones, obtained as mixtures of two diastereomers bearing four stereogenic centers with good diastereoselectivities of up to 90% de, combined with high yields, and enantioselectivities of up to 99% ee, starting from cyclohexane-1,2-diones and nitroalkenes. Nevertheless, this process was limited to cyclohexane-1,2-diones. In the same area, Zhong *et al.* have developed highly enantio- and diastereoselective domino Michael–Henry reactions of nitroalkenes with 1,3-dicarbonyl compounds, such as 2-carboxymethyl-1,4-cyclohexanedione (**56**), which provided a range of chiral bicyclo[3.2.1]octan-8-ones **57** bearing four stereogenic centers, including two quaternary stereocenters [91]. These products were produced in high yields, and enantioselectivities of up to 96% ee, with a remarkable general diastereoselectivity of >98% de (Scheme 37.10). The process was induced by cinchona alkaloid thiourea **58**, which was employed at only 5 mol% catalyst loading.



56

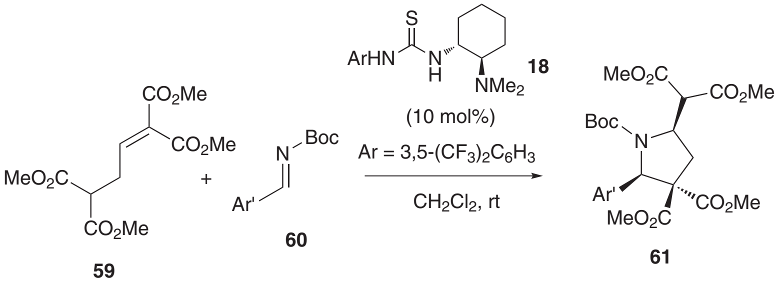
de >98%

R	Yield (%)	ee (%)
Ph	93	94
m-MeOC$_6$H$_4$	84	95
p-MeOC$_6$H$_4$	79	90
o-ClC$_6$H$_4$	86	96
p-ClC$_6$H$_4$	93	95
2-Fu	84	92
1-Naph	85	94

Scheme 37.10 Synthesis of bicyclo[3.2.1]octan-8-ones through a domino Michael–Henry reaction.

37.2.2.2 Miscellaneous Domino Reactions

The classic direct Mannich reaction, discovered in 1912 [92], is an aminoalkylation of carbonylic compounds involving ammonia (or a primary or secondary amine derivative), a non-enolizable aldehyde (usually formaldehyde) or a ketone, and an enolizable carbonyl compound, leading to β-aminocarbonyl derivatives [93]. The indirect version of the Mannich reaction is the corresponding two-component reaction of a preformed imine and an enolizable carbonyl compound. Early examples of asymmetric domino reactions initiated by the Mannich reaction were successfully developed by several groups by using, in particular, L-proline as organocatalyst [94]. Recently, Enders *et al.* developed an asymmetric domino Mannich–aza-Michael reaction, involving γ-malonate-substituted α,β-unsaturated ester **59** and *N*-Boc-protected arylaldimines **60** as the substrates [95]. As shown in Scheme 37.11, the reaction catalyzed by bifunctional thiourea **18** afforded the corresponding 2,5-*cis*-configured polysubstituted pyrrolidines **61** in good to excellent yields (76–99%) and enantioselectivities (75–94% ee) combined with an excellent diastereoselectivity of >95% de.



Ar' = Ph: 95% ee = 84%
Ar' = *o*-Tol: 91% ee = 75%
Ar' = *p*-FC$_6$H$_4$: 91% ee = 83%
Ar' = *p*-MeOC$_6$H$_4$: 99% ee = 78%
Ar' = 1-Naph: 85% ee = 83%

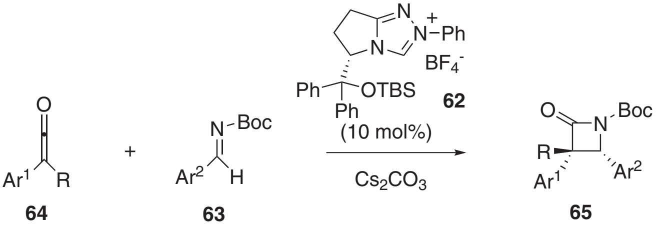
de >95%

Scheme 37.11 Synthesis of pyrrolidines through a domino Mannich–aza-Michael reaction.

Although there are many reports in the field of the enantioselective aza-Morita–Baylis–Hillman reaction, which is known to be a useful and atom-economical C–C bond-forming reaction of electron-deficient alkenes with imines usually catalyzed by Lewis bases [96], rare examples of asymmetric domino reactions initiated by this reaction have been reported. In 2010, Sasai *et al.* developed the first organocatalyzed asymmetric domino aza-Morita–Baylis–Hillman–aza-Michael reaction of α,β-unsaturated carbonyl compounds with *N*-tosylimines, allowing easy access to chiral *cis*-1,3-disubstituted isoindolines as single diastereomers [97]. The process was induced by the BINOL-derived phosphine catalyst (*S*)-2-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol, providing the five-membered products in high yields and enantioselectivities of up to 93% ee. The asymmetric Friedel–Crafts reaction is one of the most powerful methods by which to synthesize optically active aromatic compounds, and chiral Brønsted acids have recently emerged as efficient catalysts of this process [98]. In 2009, You *et al.* reported the synthesis of chiral five-membered fluorene derivatives on the basis of an asymmetric domino double Friedel–Crafts reaction catalyzed by a chiral phosphoric acid derived from BINOL [99]. This reaction involved indoles and 3′,5′-dimethoxybiphenyl-2-carbaldehyde as substrates, affording the corresponding five-membered fluorenes in moderate to high yields and enantioselectivities of up to 94% and 96% ee, respectively. In 2005, Calter *et al.* reported the synthesis of furans through an interrupted Feist–Benary reaction, occurring between α-bromopyruvates and 1,3-dicarbonyl compounds under catalysis by cinchona alkaloids such as quinine [100]. The process began with a dicarbonyl attack to the pyruvate followed by an intramolecular cyclization, rendering the final furans in good yields and enantioselectivities of up to 98% ee. In another area, MacMillan *et al.* have developed a total synthesis of the natural tetracyclic product (+)-minfiensine, including two five-membered cycles on the basis of a novel organocatalytic domino Diels–Alder–amine cyclization reaction catalyzed by a chiral imidazolidinone [101]. In another context, Dixon *et al.* have reported that the reaction of enol lactones with tryptamines, performed in the presence of 3,3′-bis(triphenylsilyl)-(*R*)-BINOL phosphoric acid, led to the formation of a set of chiral tetracyclic products including two five-membered cycles in moderate to excellent yields (63–99%) and enantioselectivities (72–99% ee) through a domino amidation–*N*-acyliminium cyclization reaction [102]. In 2007, Bode *et al.* reported the asymmetric synthesis of *cis*-1,3,4-trisubstituted cyclopentenes on the basis of the annulation of enals by 4-oxoenoates promoted by chiral triazolium-derived N-heterocyclic carbene catalysts [103]. Excellent levels of enantio-induction of up to 99% ee were achieved in combination with moderate to good yields (25–93%) and diastereoselectivities (66–90% de). Later, the same authors developed the asymmetric annulation of enals and an α-hydroxy enone catalyzed by another chiral triazolium-derived N-heterocyclic carbene catalyst to afford the corresponding cyclopentane-fused lactones with a high excellent enantioselectivity of 99% ee, high yields, and moderate diastereoselectivities (≤40% de) [104]. In addition, Ramachary *et al.* have successfully developed the asymmetric domino aldol–hemiacetalization reaction of simple ketones with a range of 2-hydroxybenzaldehydes catalyzed by *trans*-4-OH-L-proline. The reaction provided the corresponding chiral five-membered lactols in moderate yields and enantioselectivities (26–90% ee) [105]. On the other hand, a range of chiral 4,5-disubstituted isoxazoline-*N*-oxide products have been obtained by Jorgensen *et al.* through two novel asymmetric domino Henry reaction–cyclization reactions of *in situ* generated α-brominated aldehydes with ethyl nitroacetate, and of *in situ* generated epoxides with *t*-butyl nitroacetate, respectively [106]. Remarkable enantioselectivities of up to 99% ee were obtained combined with moderate yields in both cases of domino reactions, which involved chiral diarylprolinol trimethylsilyl ether **21** as catalyst. A diastereoselectivity of >90% de was obtained for the domino reaction of α-brominated aldehydes, whereas moderate diastereoselectivities (≤56% de) were obtained for the domino reaction of epoxides.

37.3
Organocatalytic Asymmetric Synthesis of Four-Membered Cycles

In recent years, asymmetric synthesis based on [2+2] cycloadditions of ketenes (discovered 100 years ago [107]) with carbonyl compounds to form chiral β-lactones has been achieved with high yields and high stereoselectivities [108]. The earliest examples based on organocatalysis have been known for almost three decades, and involve cinchona alkaloid-catalyzed asymmetric [2+2] cycloadditions between ketenes and aldehydes, providing the corresponding β-lactones. The seminal studies by Wynberg and Staring on the quinidine-catalyzed [2+2] cycloaddition of ketene with chloral were disclosed in 1982, providing the first examples of chiral organocatalysis in a [2+2] cycloaddition [109]. Some years later, Calter *et al*. developed an efficient cinchona alkaloid-catalyzed methodology for the asymmetric dimerization of pyrolytically generated methylketene and employed the resulting highly enantioenriched β-lactone in the synthesis of various biologically relevant polypropionates [110]. Later, the scope of this reaction was extended to various ketenes, generated *in situ* from acid chlorides [111]. To obtain more easily isolable products, the authors prepared *in situ* the corresponding Weinreb amides, affording the final compounds in moderate to good yields and excellent enantioselectivities (91–97% ee). In 2010, Mandoli *et al.* reported the same reaction using, as catalysts, dimeric cinchona alkaloid derivatives on a polystyrene support [112]. The process afforded the corresponding cycloadducts in good yields and excellent enantioselectivities. Armstrong *et al.* have reported the synthesis of *trans*-β-lactone carboxylates starting from ethyl glyoxylate and substituted ketenes. The reaction was efficiently catalyzed by dihydroquinidine esters at low temperatures, rendering the final lactones in very good enantioselectivities [113]. In 2001, Romo *et al.* developed an intramolecular formal [2+2] cycloaddition of ketenes and aldehydes, leading to bicyclic *cis*-lactones, catalyzed by quinidine derivatives [114]. In this approach, the ketene was generated starting from a carboxylic acid using Mukaiyama's reagent. A cinchona alkaloid catalyst turned out to be highly stereoselective, since it allowed the cycloadducts to be yielded in high enantioselectivities of up to 92% ee. Interestingly, changing the catalyst to β-isocupreidine resulted in a complete reversal of enantioselectivity with identical levels of asymmetric induction. On the other hand, even though aza-β-lactams have attracted interest because of their biological activities, only limited progress has been reported with regard to the enantioselective synthesis of this family of heterocycles. The Staudinger [2+2] cycloaddition of ketenes with imines is a versatile and efficient route by which to construct β-lactams. Although several chiral auxiliary-based asymmetric Staudinger processes have been described, there are only a few organocatalytic enantioselective examples in the literature. For example, Lectka *et al.* demonstrated that, using a quinine derivative as catalyst, the highly stereoselective coupling of a range of monosubstituted ketenes, as well as a symmetrically disubstituted ketenes, with imines could be achieved [115]. Soon afterwards, Fu *et al.* reported a highly enantioselective Staudinger cycloaddition catalyzed by planar chiral ferrocenes, which allowed the formation of chiral lactams in high yields (81–94%) and enantioselectivities (84–92% ee) [116]. More recently, Ye *et al.* demonstrated for the first time that chiral N-heterocyclic carbenes could also be efficient catalysts for the asymmetric version of this reaction [117]. The carbene was obtained by deprotonation of the suitable precursor in the presence of the imine, and the ketene was added at the end of the process. Therefore, in the presence of chiral triazolium salt **62** derived from L-pyroglutamic acid, the reaction of *N*-Boc imines **63** with ketenes **64** afforded the expected *N*-Boc β-lactams **65** in good yields, moderate to high *cis*-diastereoselectivities of up to 98% de, and excellent enantioselectivities (91–99% ee) (Scheme 37.12). At the same time, a related protocol was reported by Smith *et al.* based on the use of the another triazolium salt (**66**, Figure 37.5) in the [2+2] cycloaddition of *N*-tosyl imines with diphenylketene in the presence of KHMDS (potassium hexamethyldisilazide) as a base, providing the corresponding *N*-Ts β-lactams in excellent yields albeit with moderate enantioselectivities (≤75% ee) [118]. In addition, enantiopure imidazolinium-dithiocarboxylates such as **67** (Figure 37.5) have been found to be efficient catalysts in the [2+2] cycloaddition of various ketenes with *N*-*para*-nosyl imines [119]. The corresponding *cis*-*N*-*para*-nosyl β-lactams were obtained as major diastereomers in excellent yields (76–99%) and moderate to good diastereoselectivities (≤78% de) combined with high enantioselectivities of up to 96% ee.



Ar^1 = Ph, Ar^2 = *o*-ClC_6H_4, R = Et: 71% de = 82% ee = 99%
Ar^1 = Ph, Ar^2 = *o*-BrC_6H_4, R = Et: 58% de = 88% ee = 97%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = *o*-ClC_6H_4, R = Et: 78% de = 86% ee = 91%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = 2,4-$Cl_2C_6H_3$, R = Et: 62% de = 78% ee = 96%
Ar^1 = *p*-ClC_6H_4, Ar^2 = *o*-ClC_6H_4, R = Et: 61% de = 98% ee = 97%
Ar^1 = Ph, Ar^2 = 2,4-$Cl_2C_6H_3$, R = Me: 53% de = 72% ee = 93%

Scheme 37.12 Synthesis of *N*-Boc β-lactams through [2+2] cycloaddition of *N*-Boc-imines and ketenes catalyzed by a N-heterocyclic carbene (TBS = *tert*-butyldimethylsilyl).

β-Sultams, which are biologically interesting sulfonyl analogues of β-lactams, have been prepared by Peters and Zajac through an organocatalytic asymmetric formal [2+2] cycloaddition approach based on the reaction between non-nucleophilic imines with alkyl sulfonyl chlorides [120]. In the case of very electron-poor *N*-tosyl imines derived from chloral, the reaction with sulfonyl chlorides was catalyzed by

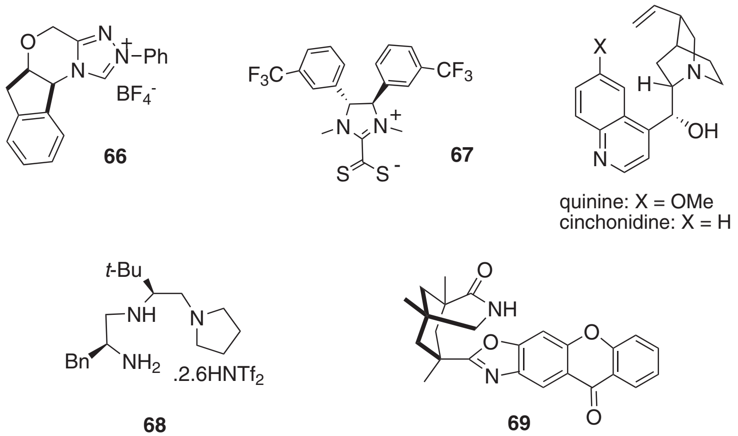


Figure 37.5 Organocatalysts used in [2+2] cycloadditions.

cinchona alkaloids such as quinine or cinchonidine (Figure 37.5), providing the corresponding β-sultams in high yields and enantioselectivities of up to 94% ee, combined with good diastereoselectivities (82–90% de).

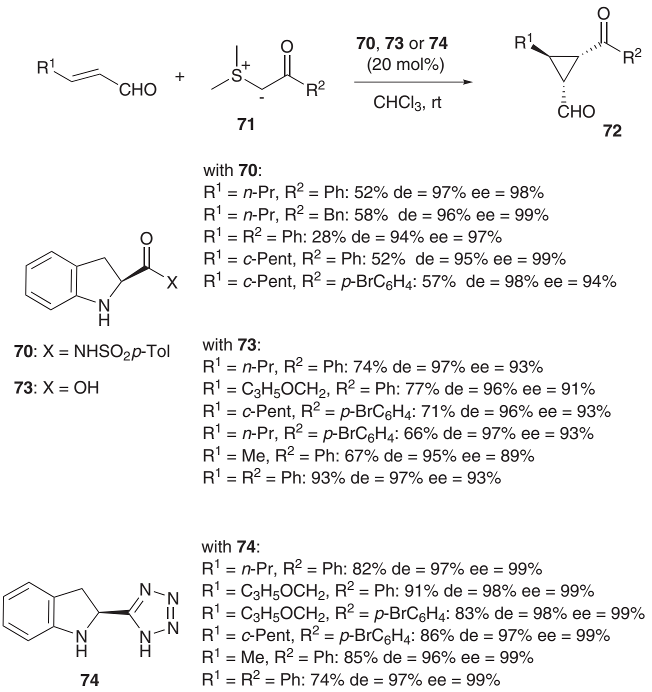
In contrast, there are only a few examples of catalytic enantioselective [2+2] cycloadditions for the synthesis of optically active cyclobutanes or cyclobutenes [121]. In 2007, Ishihara and Nakano reported the first organocatalytic asymmetric formal [2+2] cycloaddition of unactivated alkenes with α-acyloxyacroleins, providing the corresponding 1-acyloxycyclobutanecarbaldehydes [122]. This reaction was catalyzed by the ammonium salt of chiral triamine **68** (Figure 37.5). Moreover, cyclic trialkylethenes were reacted with α-(fluorobenzoyloxy)acroleins to give the corresponding four-membered cycles in moderate to good yields combined with high enantioselectivities of up to 90% ee. In contrast, 1,1- and 1,2-dialkylethenes showed no reactivity. However, the cycloaddition of 1-methylstyrene with α-benzoyloxyacrolein led to the corresponding *anti*-cycloadduct with 80% ee, albeit in low yield (20%). In all cases of substrates studied, the reaction was *anti*-stereoselective with diastereoselectivity of up to 92% de. Any reaction pathway requiring photochemical but not thermal activation is inherently impossible to catalyze with a classical organocatalyst unless the process of photochemical activation and catalysis are separated. Processes in which light energy serves as the direct driving force for enantioselective bond formation require the design of chiral organocatalysts to harvest light and allow sensitization of the substrate by energy or electron transfer [123]. In 2009, Bach *et al.* reported the synthesis of a chiral xanthone that combined significant rate acceleration by triplet energy transfer with high enantioselectivities [124]. The studied reaction was an intramolecular [2+2] photocycloaddition of 4-(3-butenyloxy)quinolone, which afforded upon catalysis with catalyst **69** (Figure 37.5) a mixture of two regioisomeric products in enantioselectivities of up to 91% ee.

37.4
Organocatalytic Asymmetric Synthesis of Three-Membered Cycles

37.4.1
Synthesis of Cyclopropanes

Organic chemists have always been fascinated by the cyclopropane subunit [125], which has played and continues to play a prominent role in organic chemistry [126]. While the cyclopropane ring is a highly strained entity, it is nonetheless found in a wide variety of naturally occurring compounds, including terpenes, pheromones, fatty acid metabolites, and unusual amino acids [127]. Indeed, the prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis [128]. The first example of enantioselective organocatalytic synthesis of cyclopropanes was developed by MacMillan *et al.*, in 2005 [129]. This methodology dealt with the reaction of enals with benzoylmethyl sulfonium ylides to afford the corresponding cyclopropanes. In the catalyst screening, MacMillan realized that, in the transition state, the iminium ion and the ylide might engage in an electrostatic association via the pendant carboxylate and the thionium substituents, respectively. In this scenario, MacMillan's imidazolidinones were electronically averse to this association and were revealed to be inert in the reaction. The use of proline provided good levels of reaction efficiency (72% conversion) but moderate enantiocontrol (46% ee). The authors assumed that the zwitterionic iminium ion derived from proline could readily populate both (*E*)- and (*Z*)-iminium isomers. This equilibrium led to a diminished enantiocontrol. To overcome this limitation, MacMillan used chiral dihydroindole 2-carboxylic acid as catalyst. To minimize the repulsive steric interaction between the olefinic substrate and the arylic hydrogen, the iminium ion predominantly adopted a (*Z*)-configuration, increasing the enantiocontrol up to 96% ee. More recently, Arvidsson *et al.* have developed novel aryl sulfonamides derived from (2*S*)-indoline-2-carboxylic acid, such as **70**, which were used as catalysts to promote the reaction between a range of enals and sulfur ylides **71**, providing the corresponding cyclopropanes **72** in moderate to good yields and both excellent diastereo- and enantioselectivities of 94–98% de and 88–99% ee, respectively (Scheme 37.13) [130]. Moreover, these reactions were also investigated upon catalysis with other (2*S*)-indoline-2-carboxylic acid derivatives, such as (*S*)-(−)-indoline-2-carboxylic acid **73**, and (*S*)-(−)-indoline-2-yl-1*H*-tetrazole **74** [131]. Higher yields for the corresponding cycloadducts **72** were obtained with both catalysts, combined with remarkable diastereo- and enantioselectivities of up to 98% de and 99% ee, respectively (Scheme 37.13).

In the same area, Xiao *et al.* have developed asymmetric cyclopropanations of β,γ-unsaturated α-ketoesters with stabilized sulfur ylides catalyzed by C_2-symmetric ureas [132]. Although the stereoselectivities had to be further improved (de ≤82% and ee ≤80%), this novel methodology opened up access to other highly functionalized 1,2,3-trisubstituted cyclopropanes. In 2007, Cao *et al.* reported a novel



71

72

70: X = $NHSO_2p$-Tol

73: X = OH

74

with **70**:
R^1 = *n*-Pr, R^2 = Ph: 52% de = 97% ee = 98%
R^1 = *n*-Pr, R^2 = Bn: 58% de = 96% ee = 99%
R^1 = R^2 = Ph: 28% de = 94% ee = 97%
R^1 = *c*-Pent, R^2 = Ph: 52% de = 95% ee = 99%
R^1 = *c*-Pent, R^2 = *p*-BrC_6H_4: 57% de = 98% ee = 94%

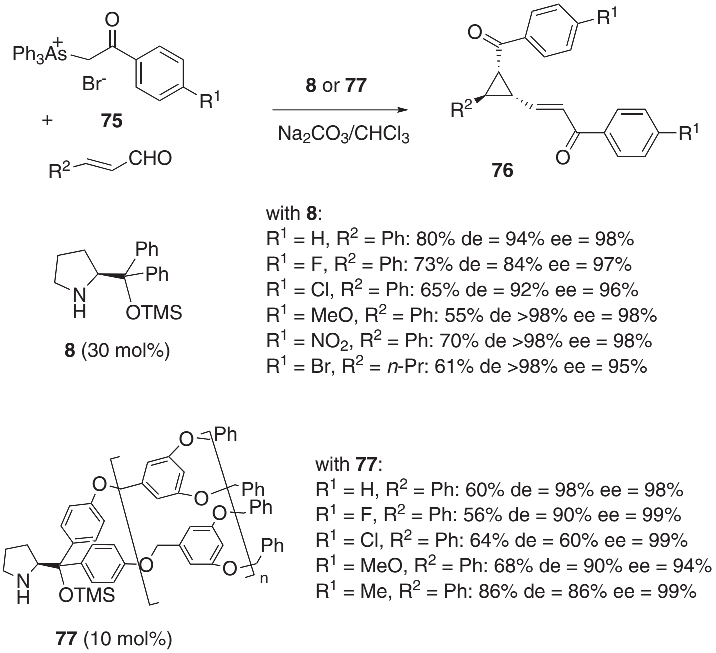
with **73**:
R^1 = *n*-Pr, R^2 = Ph: 74% de = 97% ee = 93%
R^1 = $C_3H_5OCH_2$, R^2 = Ph: 77% de = 96% ee = 91%
R^1 = *c*-Pent, R^2 = *p*-BrC_6H_4: 71% de = 96% ee = 93%
R^1 = *n*-Pr, R^2 = *p*-BrC_6H_4: 66% de = 97% ee = 93%
R^1 = Me, R^2 = Ph: 67% de = 95% ee = 89%
R^1 = R^2 = Ph: 93% de = 97% ee = 93%

with **74**:
R^1 = *n*-Pr, R^2 = Ph: 82% de = 97% ee = 99%
R^1 = $C_3H_5OCH_2$, R^2 = Ph: 91% de = 98% ee = 99%
R^1 = $C_3H_5OCH_2$, R^2 = *p*-BrC_6H_4: 83% de = 98% ee = 99%
R^1 = *c*-Pent, R^2 = *p*-BrC_6H_4: 86% de = 97% ee = 99%
R^1 = Me, R^2 = Ph: 85% de = 96% ee = 99%
R^1 = R^2 = Ph: 74% de = 97% ee = 99%

Scheme 37.13 Synthesis of functionalized cyclopropanes through [2+1] cycloaddition of sulfur ylides and enals (Pent = pentyl).

cyclopropanation of enals with arsonium ylides **75**, using amine **8** as catalyst, which furnished the corresponding [2+1] cycloadducts **76** in moderate to good yields combined with both excellent diastereo- and enantioselectivities of >98% de and 98% ee, respectively (Scheme 37.14) [133]. Furthermore, the scope of this methodology was extended to the use of chiral 2-trimethylsilanyloxy-methyl-pyrrolidine-based dendritic catalyst **77**, allowing recovery of the catalyst and its reusability [134]. This process provided cyclopropanes in excellent enantioselectivities of up to 99% ee, with good to high diastereoselectivities and good yields (Scheme 37.14).

In contrast to the use of the specific type of sulfur ylides and related compounds, the employment of readily available alkyl halides for a catalytic Michael–alkylation reaction with enals to produce the corresponding formal [2+1] cycloadducts is an extremely challenging task. As an example, Wang [82a] and Cordova [82b, 83a] independently reported the enantioselective organocatalytic reaction of bromomalonates **78** and enals, which led to the corresponding cyclopropanes **79**. In both cases, chiral diarylprolinol trimethylsilyl ethers **8** and **80** were involved as catalysts, giving access to the corresponding 2-formylcyclopropane derivatives **79** in



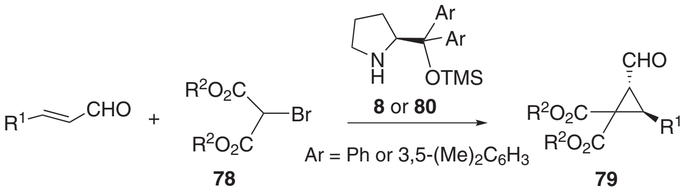
with **8**:
R^1 = H, R^2 = Ph: 80% de = 94% ee = 98%
R^1 = F, R^2 = Ph: 73% de = 84% ee = 97%
R^1 = Cl, R^2 = Ph: 65% de = 92% ee = 96%
R^1 = MeO, R^2 = Ph: 55% de >98% ee = 98%
R^1 = NO_2, R^2 = Ph: 70% de >98% ee = 98%
R^1 = Br, R^2 = *n*-Pr: 61% de >98% ee = 95%

with **77**:
R^1 = H, R^2 = Ph: 60% de = 98% ee = 98%
R^1 = F, R^2 = Ph: 56% de = 90% ee = 99%
R^1 = Cl, R^2 = Ph: 64% de = 60% ee = 99%
R^1 = MeO, R^2 = Ph: 68% de = 90% ee = 94%
R^1 = Me, R^2 = Ph: 86% de = 86% ee = 99%

Scheme 37.14 Synthesis of functionalized cyclopropanes through the [2+1] cycloaddition of enals and arsonium ylides.

excellent diastereo- and enantioselectivities (Scheme 37.15). One merit of these novel methodologies was highlighted by their high efficiency in producing heavily functionalized cyclopropanes bearing two stereogenic centers along with a quaternary carbon center.

In the same context, the addition of 2-bromoketoesters to enals was developed by Rios *et al.* in the presence of TEA as a base in toluene at 4 °C producing, upon catalysis with amine **8**, the corresponding formal [2+1] cycloadducts in high yields of up to 95% and diastereoselectivities >92% de combined with enantioselectivities of up to 99% ee [135]. To make this type of reaction even more interesting from an environmental point of view, Vicario *et al.* have recently demonstrated that it was possible to react diethyl bromomalonate and enals in water at room temperature (rt) without using an external base [136]. The reaction, catalyzed by a chiral diarylprolinol trimethylsilyl ether, proceeded efficiently when β-aryl-substituted α,β-unsaturated aldehydes were employed as substrates, while it failed when aliphatic enals were used. The corresponding formal cycloadducts were formed with enantioselectivities of up to >99% ee combined with good yields of up to 84%. In addition, amine **8** was applied as catalyst to the enantioselective cyclopropanation of α-substituted α,β-unsaturated aldehydes with diethyl bromomalonate,



with Ar = Ph, (10 mol% of **8**), in CH_2Cl_2 at 0°C with 2,6-lutidine:
R^1 = *p*-$NO_2C_6H_4$, R^2 = Me: 95% de >94% ee = 94%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Et: 87% de >94% ee = 94%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Bn: 88% de >94% ee = 93%
R^1 = *o*-$NO_2C_6H_4$, R^2 = Me: 89% de >94% ee = 96%
R^1 = *p*-FC_6H_4, R^2 = Me: 84% de >94% ee = 97%
R^1 = *o*-ClC_6H_4, R^2 = Me: 94% de >94% ee = 98%
R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 84% de >94% ee = 95%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me: 85% de >94% ee = 94%
R^1 = Ph, R^2 = Me: 88% de >94% ee = 96%
with Ar = Ph, (20 mol% of **8**), in $CHCl_3$ at rt with TEA:
R^1 = $BnCH_2$, R^2 = Et: 74% de >92% ee = 94%
R^1 = CO_2Et, R^2 = Et: 50% de >92% ee = 93%
R^1 = 2-Naph, R^2 = Et: 83% de >92% ee = 96%
R^1 = *p*-ClC_6H_4, R^2 = Et: 60% de >92% ee = 96%
with Ar = 3,5-$(Me)_2C_6H_3$, (20 mol% of **80**), in $CHCl_3$ at rt with TEA:
R^1 = Ph, R^2 = Et: 87% de >92% ee = 99%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Et: 81% de >92% ee = 98%

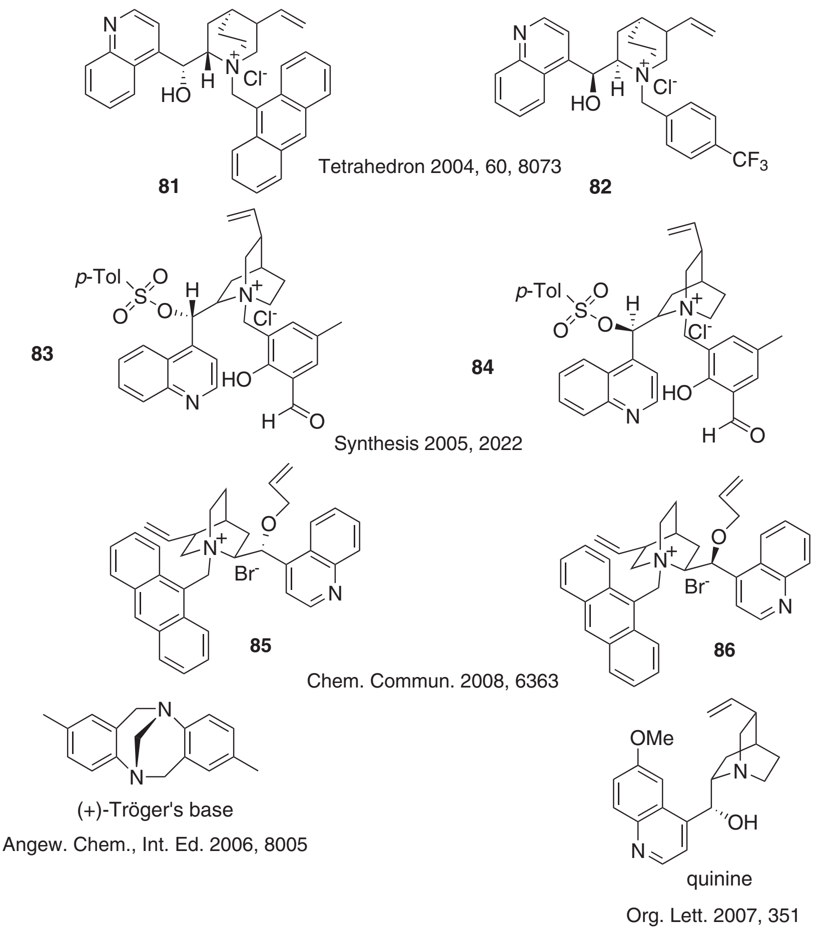
Scheme 37.15 Synthesis of functionalized cyclopropanes through [2+1] cycloaddition of bromomalonates and enals (TEA = triethylamine).

allowing efficient formation of the corresponding cyclopropanes bearing a quaternary carbon stereocenter at the α-position of the aldehyde function [137]. This nice extension of previously reported methodologies provided good yields (up to 78%) and enantioselectivities of up to 97% ee. The process was performed in ethanol at room temperature in the presence of 2,6-lutidine or *N*-methylimidazole as a base. Bromomalonates, such as diethyl bromomalonate, have also been condensed through organocatalysis onto α,β-unsaturated nitroalkenes, providing highly functionalized nitrocyclopropanes. As an example, Yan *et al*. have achieved these reactions highly enantioselectively by using 6′-demethylquinine as catalyst at a low catalyst loading of 5 mol% [138]. Indeed, a range of formal [2+1] cycloadducts could be generated as almost single *trans*-diastereomers from various aryl and heteroaryl nitroethylenes in excellent enantioselectivities of up to >99% ee combined with good yields. Besides cinchona alkaloids, Lattanzi and Russo have implicated (*S*)-α,α-di-β-naphthyl-2-pyrrolidinemethanol as another catalyst to induce the same reactions [139]. Although an almost complete *trans*-diastereoselectivity was observed, the cyclopropanes were obtained in lower enantioselectivities (≤49% ee) and by using a higher catalyst loading of 30 mol%. Moreover, a chiral thiourea was employed by Connon *et al*., in 2006, to induce the cyclopropanation of β-nitrostyrenes with 2-chloromalonates, providing the expected cyclopropanes in diastereoselectivities of >98% de, albeit the enantioselectivities remained low to moderate (14–47% ee) [140]. On the other hand, novel organocatalytic highly enantioselective nitrocyclopropanations of α,β-unsaturated carbonyl derivatives with bromonitromethane have been developed recently. Moderate to high enantioselectivities (≤90% ee) combined with good to high yields and complete diastereoselectivity were obtained by Ley *et al.* for the nitrocyclopropanation of various cyclic α,β-unsaturated enones upon catalysis with (*R*)-α-pyrrolidinyl tetrazole [82c, 141]. The scope of this methodology was extended to acyclic α,β-unsaturated enones, providing the corresponding nitrocyclopropanes with good yields combined, however, with reduced enantioselectivities (≤76% ee). Recently, Yan *et al.* have reported the same reactions under bifunctional catalysis by primary amines bearing a thiourea moiety [142]. The final compounds were obtained in good yields and excellent enantioselectivities. However, the scope of the process was narrow, allowing only the use of cyclic enones. In contrast, bromonitromethane could be reacted highly efficiently with acyclic α,β-unsaturated enones by using the salt of 9-amino-deoxyepiquinine as catalyst in the presence of *trans*-dimethylpiperazine to mediate the final cyclization, as reported by Wang *et al.* [143]. Indeed, the corresponding nitrocyclopropanes were produced in remarkable levels of enantio- and diastereoselectivities of up to >99% ee and 92% de, respectively. Application of this catalyst in the presence of *N*-methylmorpholine as an additive to the reaction of various cyclic enones also gave remarkable results for both the yields and enantioselectivities, along with a complete diastereoselectivity, since the corresponding formal cycloadducts were isolated in high yields (83–99%) and enantioselectivities of up to >99% ee. In addition, Cordova *et al.* have developed the first example of a highly enantioselective organocatalytic nitrocyclopropanation of enals with bromonitromethane [144]. The best results were obtained by using amine **8** as catalyst combined with TEA as a base, which afforded a set of 1-nitro-2-formylcyclopropanes bearing three stereogenic centers as a mixture of two diastereomers with moderate to good yields (≤63%) and moderate diastereoselectivities of up to 50% de, combined with excellent enantioselectivities (92–99% ee). A total synthesis of eicosanoid was developed by Kumaraswamy and Padmaja in which the chirality originated through an organocatalytic cyclopropanation using a quinidine-based alkaloid [145]. On the other hand, Takemoto *et al.* have investigated a chiral bifunctional thiourea to promote the nitrocyclopropanation of bromonitromethane with α-cyano-α,β-unsaturated imides, which directly furnished a range of 2-nitrocyclopropanecarboxylic acid derivatives recognized as versatile precursors for biologically active compounds [146]. Thus, a series of highly functionalized formal [2+1] cycloadducts bearing three stereogenic centers could be prepared through this methodology in good yields of up to 81% and excellent enantioselectivities of up to 99% ee, albeit with moderate diastereoselectivities (≤46% de). Finally, the same catalyst was also employed by Fan *et al.* to induce an efficient oxidative cyclopropanation of the Michael adducts of nitroolefins with activated methylene compounds by using the combination of iodobenzene diacetate and tetrabutylammonium iodide in toluene [147]. This one-pot reaction afforded highly functionalized nitrocyclopropanes in moderate to good yields with high diastereo- and enantioselectivities of >90% de and 94% ee, respectively.

37.4.2
Synthesis of Aziridines

Aziridines are among the most important types of nitrogenated heterocycles. For a long time it was not known that organocatalysts could be used to catalyze aziridinations [148]. In recent years, several examples of the organocatalytic enantioselective aziridination of activated olefins, such as enones or enals, have been successfully developed by employing a range of organocatalysts (Figure 37.6) and these reactions have become a topic of interest in asymmetric organocatalysis. Among these processes are those based on the use of quaternary salts of cinchona alkaloids such as **81** and **82** (Figure 37.6), for inducing chirality in the aziridination of 2-(phenylsulfanyl)-2-cycloalkenones [149]. In this work, reported by Tardella *et al.* in 2004, it was shown that the reaction of these cycloalkenones with ethyl nosyloxycarbamate under phase-transfer conditions provided the corresponding aziridines in satisfactory yields (18–93%) and moderate to good enantioselectivities (25–75% ee). Soon after this, Murugan and Siva developed other cinchona alkaloids as chiral phase-transfer catalysts, such as **83** and **84** (Figure 37.6), to be applied to the aziridination of a wide range of electron-deficient olefins with *N*-acyl-*N*-aryl hydroxamic acids [150]. The corresponding chiral *N*-arylaziridines were isolated in moderate to good yields (49–92%) and enantioselectivities (49–95% ee). In 2008, Minakata *et al.* reported a new method for the aziridination of electron-deficient olefins based on the use of *N*-chloro-*N*-sodio carbamates [151]. These reactions were promoted by phase-transfer chiral ammonium salt catalysts **85** and **86** derived from cinchona alkaloids (Figure 37.6), yielding the corresponding aziridines from α,β-unsaturated ketones, esters, sulfones, and amides in good yields (62–98%) and with enantioselectivities of up to 86% ee. In 2006, Shi *et al.* reported a one-pot process that involved the *in situ* generation of a hydrazinium salt, deprotonation of the hydrazinium to form an aminimide, and subsequent aziridination by reaction with chalcones [152]. It was shown that *O*-mesitylenesulfonylhydroxylamine could readily aminate various tertiary amines to give the corresponding hydrazinium salts in high yields. The asymmetric aziridination of chalcones was then examined by treating *O*-mesitylenesulfonylhydroxylamine and a chiral tertiary amine such as (+)-Tröger's base (Figure 37.6), associated with $CsOH.H_2O$ as a base. A reasonable level of enantioselectivity of up to 67% ee could be obtained by applying these conditions to the aziridination of two chalcones. In the same context, Armstrong *et al.* have developed the asymmetric aziridination of chalcone using an aminimide generated *in situ* from the treatment of a chiral tertiary amine, such as quinine (Figure 37.6), with *O*-(diphenylphosphinyl)hydroxylamine, which provided a promising level of asymmetric induction of 56% ee for the aziridination of (*E*)-chalcone [153].

An unprecedented example of a highly chemo- and enantioselective organocatalytic aziridination of enals with acylated hydroxycarbamates was reported by



81

Tetrahedron 2004, 60, 8073

82

83

Synthesis 2005, 2022

84

85

Chem. Commun. 2008, 6363

86

(+)-Tröger's base

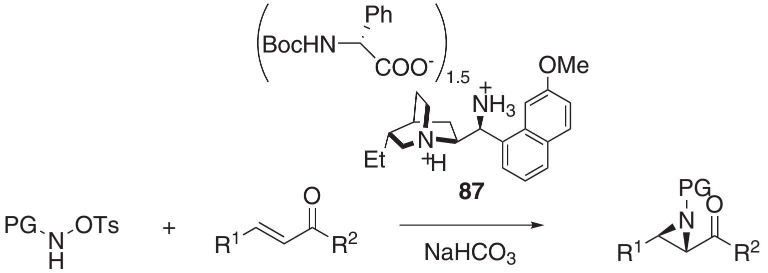
Angew. Chem., Int. Ed. 2006, 8005

quinine

Org. Lett. 2007, 351

Figure 37.6 Organocatalysts used in the aziridination of activated alkenes (Tol = tolyl).

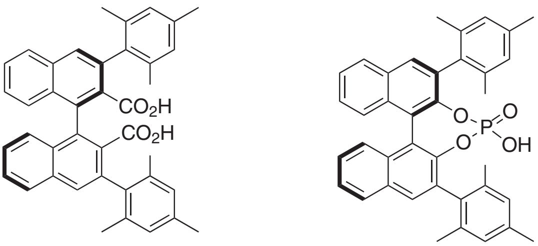
Cordova *et al.*, in 2007 [154]. This reaction was efficiently catalyzed by simple chiral pyrrolidine derivatives such as amine **8** and led to the corresponding 2-formylaziridines in good yields with diastereoselectivities of up to 90% de and enantioselectivities of up to 99% ee. In 2009, Hamada *et al.* reported an interesting variation on this process, employing *N*-arenesulfonyl-carbamates as the nitrogen source combined with 3 equivalents of a base and (*S*)-diphenylprolinol triethylsilyl ether **33** [155]. This protocol improved both the chemical yields (51–99%) and the diastereoselectivities (80–98% de), while maintaining the excellent enantiocontrol (91–99% ee) in comparison with the previous method developed by Cordova. Moreover, this methodology expanded the scope of aldehydes, allowing the aziridination of aromatic enals with total diastereoselectivity. A closely related strategy was applied by Melchiorre *et al.* to the aziridination of enones by using chiral primary amine salt **87** as catalyst, which was prepared by combining easily available 9-amino(9-deoxy)-*epi*-hydroquinine with D-*N*-Boc-phenylglycine [156]. Therefore, both linear and cyclic enones reacted with tosylated hydroxycarbamates to afford the corresponding aziridines with almost complete diastereocontrol and very high enantioselectivity of up to 99% ee (Scheme 37.16). These results showed the ability of this chiral organocatalyst salt to promote an asymmetric domino iminium–enamine intramolecular sequence.



$R^1 = n$-Pent, R^2 = Me, PG = Cbz: 93% de = 90% ee = 96%
$R^1 = n$-Pent, R^2 = Me, PG = Boc: 82% de >90% ee = 99%
$R^1 = R^2$ = Me, PG = Cbz: 96% de >90% ee = 93%
R^1 = Me, R^2 = Et, PG = Cbz: 94% de = 90% ee = 98%
$R^1 = CO_2Et$, R^2 = Me, PG = Cbz: 85% de >90% ee = 73%
R^1 = Ph, R^2 = Me, PG = Cbz: 85% de >90% ee = 99%
$R^1 = p$-$NO_2C_6H_4$, R^2 = Me, PG = Cbz: 92% de >90% ee = 99%
$R^1,R^2 = (CH_2)_3$, PG = Cbz: 86% de >90% ee = 98%

Scheme 37.16 Synthesis of aziridines through the aziridination of enones with tosylated hydroxycarbamates (PG = protecting group, Ts = tosyl, i.e., 4-toluenesulfonyl).

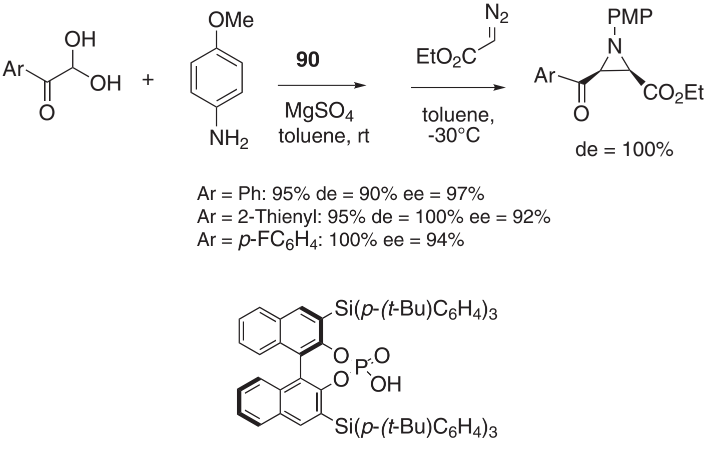
Another methodology used to obtain chiral aziridines is based on the enantioselective aza-Darzens reaction with diazo compounds. An enantioselective organocatalytic aza-Darzens reaction with diazo compounds was not achieved until 2008, when Maruoka *et al.* reported the first enantioselective *trans*-aziridination of diazoacetamides with *N*-Boc imines catalyzed by chiral dicarboxylic acids such as **88** (Figure 37.7) [157]. Despite the limitation of this methodology to aromatic imines, the desired *trans*-aziridines were obtained in good yields (51–61%), moderate to good diastereoselectivities (46–80% de), and excellent enantioselectivities (97–99% ee). In 2009, Zhong *et al.* reported the same reaction using chiral phosphoric acid derivatives, such as **89** (Figure 37.7), instead of dicarboxylic acids, which furnished chiral *trans*-aziridines in excellent yields (90–97%) and high diastereoselectivities (>90% ee) combined with high enantioselectivities (88–93% ee) [158].



88 **89**

Figure 37.7 Organocatalysts used in the aza-Darzens reaction.

At almost the same time, Akiyama *et al.* developed a similar aza-Darzens reaction using aldimines derived from aryl glyoxals and ethyl diazoacetate promoted by chiral BINOL-derived phosphoric acid catalysts, such as **90** (Scheme 37.17) [159]. In this case, the reaction rendered exclusively the corresponding *cis*-aziridine carboxylates in both excellent yields (95–100%) and enantioselectivities (92–97% ee). However, the scope of the method seemed to be quite narrow since only aromatic glyoxals were employed.



Ar = Ph: 95% de = 90% ee = 97%
Ar = 2-Thienyl: 95% de = 100% ee = 92%
Ar = p-FC$_6$H$_4$: 100% ee = 94%

90

Scheme 37.17 Synthesis of aziridines through the aza-Darzens reaction (PMP = *para*-methoxyphenyl).

37.5
Conclusion

Since the seminal reports of Hajos and Parrish [4c], Eder, Wiechert, and Sauer [4b], and Woodward *et al.* [160], asymmetric organocatalysis has been providing powerful and practical methods for the highly stereocontrolled construction of a huge variety of carbo- and heterocyclic five-, four-, and three-membered compounds. Impressive levels of stereoselective control of up to five stereocenters including quaternary carbon centers have been reached by using various types of organocatalysts in intermolecular ring-forming reactions, such as cycloadditions as well as domino reactions, and are increasingly being used in enantioselective total syntheses. In the case of polycyclic systems, either fused, bridged, or spiranic ring arrangements can be accessed. The enantioselective organocatalytic formation of five-, four-, and three-membered cycles and heterocycles has opened a new avenue to medicinal chemistry since a number of these products are known to exhibit important biological activities.

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38
Diels-Alder and Hetero-Diels–Alder Reactions

Haifeng Du and Kuiling Ding

38.1
Introduction

Since the first [4+2] cycloaddition between benzoquinone and cyclopentadiene was reported by Otto P.H. Diels and Kurt Alder in 1928, the so-called Diels–Alder reaction, which can generate two σ bonds stereoselectively and up to four stereogenic centers in a single step to construct highly desirable six-membered cyclic compounds, has become one of the most useful tools in synthetic chemistry [1, 2]. In an over 80-year history, intensive and fruitful studies on the Diels–Alder reaction have focused mainly on broadening the diene and dienophile scope (such as the hetero-Diels–Alder reaction), understanding its mechanism (such as frontier molecular orbital theory), exploring its enantioselective version, and expanding its application in the total synthesis of complex molecules. Owing to the importance and the increasing demand of optically active compounds, asymmetric Diels–Alder reaction has been extensively investigated and successfully developed, from employing chiral auxiliaries to using catalytic amount of chiral catalysts. Chiral Lewis-acid catalysts dominated this field for more than 30 years [3] before the rapid growth of employing easily available and environmentally benign small chiral organic molecules as effective catalysts. Although the first successful enantioselective organocatalysis of a Diels–Alder reaction was not reported until 1989 by Kagan and coworkers [4], great progress has already been achieved [5]. The aim of this chapter is to mainly discuss the rapid development of organocatalysts for catalytic intermolecular Diels–Alder reaction, oxa-hetero-Diels–Alder reaction, and aza-hetero-Diels–Alder reaction. The application of organocatalytic Diels–Alder reactions in total syntheses and in multicomponent reactions and the asymmetric intramolecular Diels–Alder reactions are reviewed in other chapters and will not be included here.

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38.2
Organocatalytic Diels–Alder Reaction

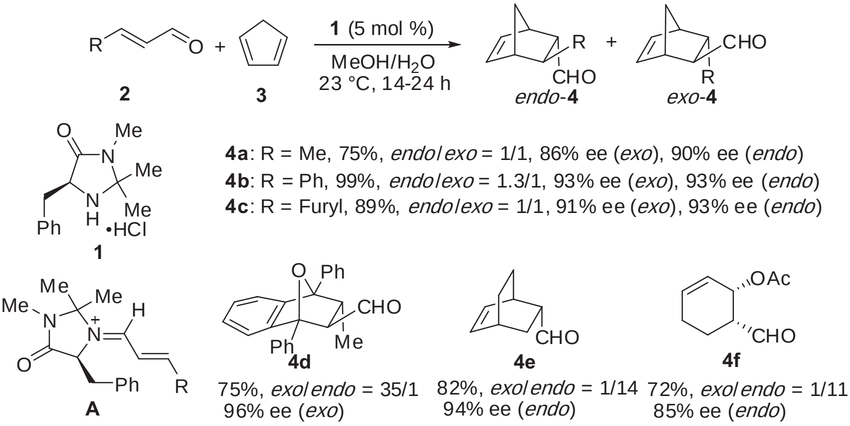
38.2.1
Chiral Secondary or Primary Amines as Catalysts

Chiral secondary or primary amines are one class of the most studied catalysts for asymmetric organocatalysis of Diels–Alder reactions, in which the amine activates α,β-unsaturated aldehydes or ketones through a covalent activation mode by forming reversible imine or enamine intermediates with the carbonyl groups. Accordingly, relatively high catalyst loadings (up to 20 mol% in some cases) are often necessary to ensure the acquisition of satisfactory activity and selectivity.

38.2.1.1 Chiral Secondary Amine

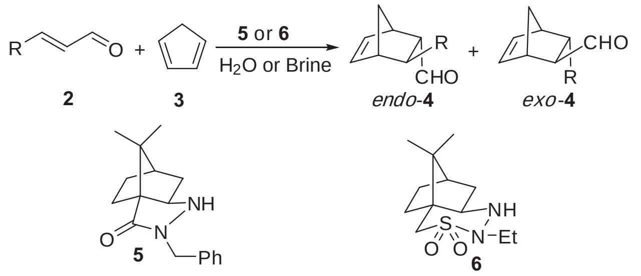
38.2.1.1.1 Imine Activation

The first highly enantioselective organocatalytic Diels–Alder reaction using secondary amine as catalyst was accomplished by the MacMillan group in 2000 [6]. They adopted a novel strategy to lower the energy of the dienophile LUMO via condensation of α,β-unsaturated aldehydes **2** with chiral amine catalyst **1**. The generated reversible iminium ion **A** was then sufficiently activated to react with diene **3** to furnish the enantioenriched cycloadducts **4**. Various α,β-unsaturated aldehydes as well as cyclic or acyclic dienes were tolerant for this transformation, providing the desired products in high yields with excellent ee's but usually with moderate diastereoselectivities (Scheme 38.1).



Scheme 38.1 The first secondary-amine-catalyzed asymmetric Diels–Alder reactions.

With the aim of increasing secondary-amine-catalyst turnover, Ogilive and coworkers disclosed the novel class of camphor-derived five-membered cyclic hydrazines **5** to enhance their nucleophilicity by means of the α-heteroatom effect [7]. With the use of this catalyst, aqueous Diels–Alder reactions proceeded efficiently to give good to excellent enantioselectivities and a preference for the *exo* isomer (Scheme 38.2). Further mechanistic studies indicate that extremely rapid iminium formation is involved. Moreover, a series of camphor-derived six-membered cyclic hydrazines **6** were also developed as effective catalysts for aqueous Diels–Alder reactions with a preference for the *endo* products (Scheme 38.2) [8].



5 (20 mol %), TfOH (20 mol %):

4a: R = Me, 74%, *endo*/*exo* = 1/1.1
72% ee (*endo*), 68% ee (*exo*)

4b: R = Ph, 96%, *endo*/*exo* = 1/1.9
88% ee (*endo*), 90% ee (*exo*)

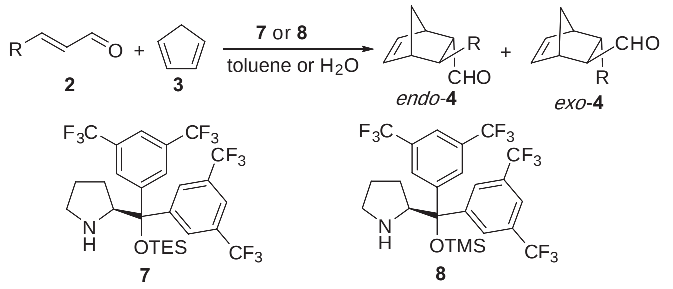
6 (20 mol %), CCl_3CO_2H (10 mol %):

4a: R = Me, 92%, *endo*/*exo* = 1.5/1
83% ee (*endo*)

4b: R = Ph, 92%, *endo*/*exo* = 1.1/1
93% ee (*endo*), 78% ee (*exo*)

Scheme 38.2 Hydrazine derived catalysts for enantioselective Diels–Alder reactions.

An *exo*-selective and highly enantioselective Diels–Alder reaction of α,β-unsaturated aldehydes was successfully realized by the Hayashi group in 2007 with the use of diarylprolinol silyl ether **7** as catalyst in combination with trifluoroacetic acid (TFA) (Scheme 38.3) [9a]. Later, the same group observed that water could



7 (10 mol %), TFA (20 mol %), in toluene

4b: R = Ph, 100%, *endo*/*exo* = 1/5.7
88% ee (*endo*), 97% ee (*exo*)

4c: R = Furyl, 67%, *endo*/*exo* = 1/4
78% ee (*endo*), 94% ee (*exo*)

4g: R = ^{n}Bu, 65%, *endo*/*exo* = 1/3.5
91% ee (*endo*), 94% ee (*exo*)

4h: R = Cy, 78%, *endo*/*exo* = 1/5.7
93% ee (*endo*), 97% ee (*exo*)

8 (5 mol %), $HClO_4$ (5 mol %), in H_2O

4b: R = Ph, 93%, *endo*/*exo* = 1/4
92% ee (*endo*), 97% ee (*exo*)

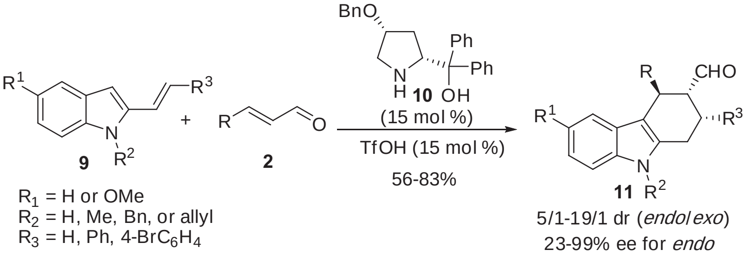
4c: R = Furyl, 76%, *endo*/*exo* = 1/3.2
84% ee (*endo*), 92% ee (*exo*)

4g: R = ^{n}Bu, 95%, *endo*/*exo* = 1/4
92% ee (*endo*), 98% ee (*exo*)

4h: R = Cy, 91%, *endo*/*exo* = 1/5.7
98% ee (*endo*), 98% ee (*exo*)

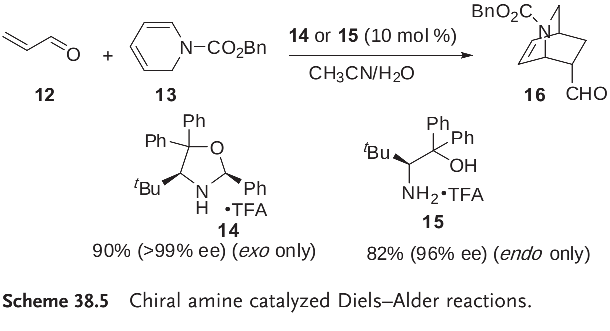
Scheme 38.3 *exo*-Selective enantioselective Diels–Alder reactions.

significantly accelerate the diarylprolinol silyl ether **8** catalyzed *exo*-selective reactions and noticeably improve the enantioselectivities (Scheme 38.3) [9b]. The effect of water is considered to be completely different from that of Breslow's homogenous reaction "in water" and that of Sharpless' "on water" reaction. Recently, Zhao and coworkers extended the application of diarylprolinol **10** in an organocatalytic Diels–Alder reaction between α,β-unsaturated aldehydes and 2-vinylindoles **9** to produce various functionalized tetrahydrocarbazoles **11** in high yields with excellent enantioselectivities (Scheme 38.4) [10].



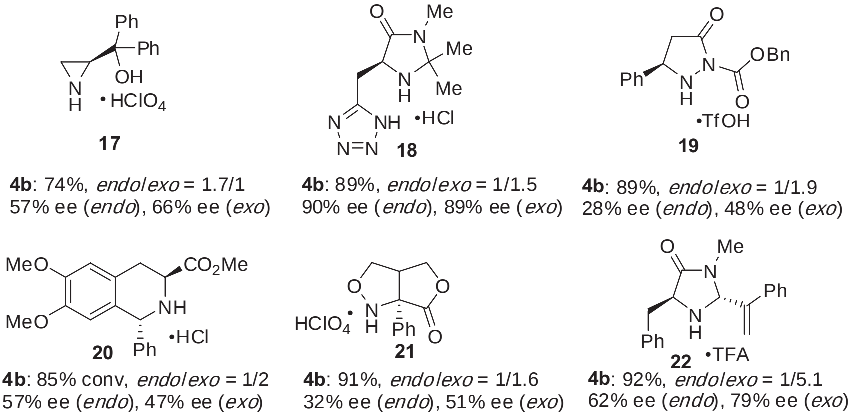
Scheme 38.4 Enantioselective Diels–Alder reactions with 2-vinylindoles.

In 2010, Nakano, Takeshita, and coworkers reported an organocatalytic Diels–Alder reaction between 1,2-dihydropyridine **13** and acrolein **12** using a chiral oxazolidine catalyst **14** to produce the chiral isoquinuclidine **16** as an important synthetic intermediate of oseltanuvir (Tamiflu) in 90% yield with >99% ee (Scheme 38.5) [11a]. A simple chiral amino alcohol catalyst **15** containing a primary amine moiety was also developed by the same group for this transformation, giving excellent enantioselectivity (Scheme 38.5) [11b].



Scheme 38.5 Chiral amine catalyzed Diels–Alder reactions.

Since MacMillan reported the first chiral secondary amine catalyst for organocatalytic Diels–Alder reactions [6], intensive studies on the development of novel



17
4b: 74%, *endo*/*exo* = 1.7/1
57% ee (*endo*), 66% ee (*exo*)

18
4b: 89%, *endo*/*exo* = 1/1.5
90% ee (*endo*), 89% ee (*exo*)

19
4b: 89%, *endo*/*exo* = 1/1.9
28% ee (*endo*), 48% ee (*exo*)

20
4b: 85% conv, *endo*/*exo* = 1/2
57% ee (*endo*), 47% ee (*exo*)

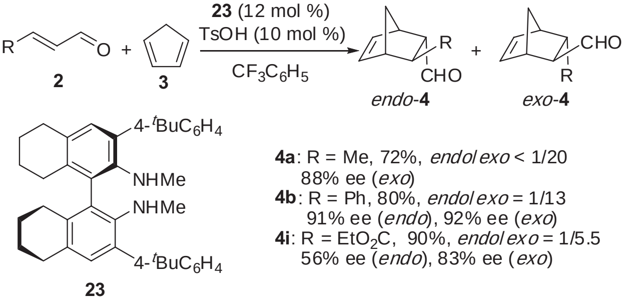
21
4b: 91%, *endo*/*exo* = 1/1.6
32% ee (*endo*), 51% ee (*exo*)

22
4b: 92%, *endo*/*exo* = 1/5.1
62% ee (*endo*), 79% ee (*exo*)

Figure 38.1 Chiral amines for the catalyzed Diels–Alder cycloaddition of cinnamaldehyde.

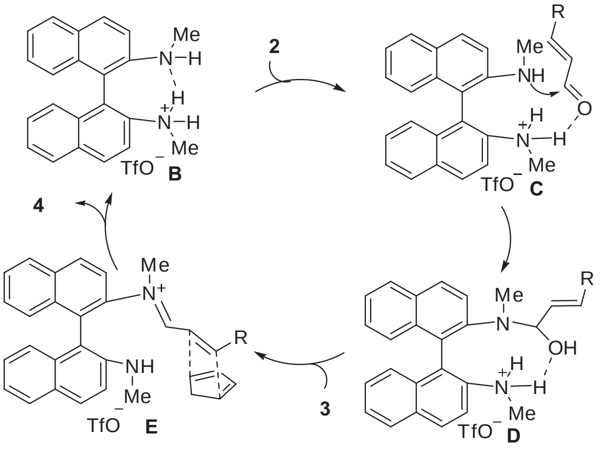
catalysts have produced several chiral amines such as **17**–**22** for the catalysis of Diels–Alder reactions between α,β-unsaturated aldehydes and dienes, affording reasonable yields and enantioselectivities (Figure 38.1) [12].

Besides the aforementioned mono-amino catalysts, chiral diamines also proved to be effective catalysts for the organocatalytic Diels–Alder reaction of α,β-unsaturated aldehydes. In 2006, the Maruoka group disclosed a highly *exo*-selective Diels–Alder reaction with the use of binaphthyl-based diamine salts **23** as organocatalysts to afford products **4** in high yields with excellent enantioselectivities (Scheme 38.6) [13]. Further studies indicate that both the amino groups of **23** are essential for the obtained high reactivity, and a plausible mechanism has been provided. As shown in Scheme 38.7, the role of free amino group is to assist the formation of the iminium ion **E** between the carbonyl group and the other amino group.



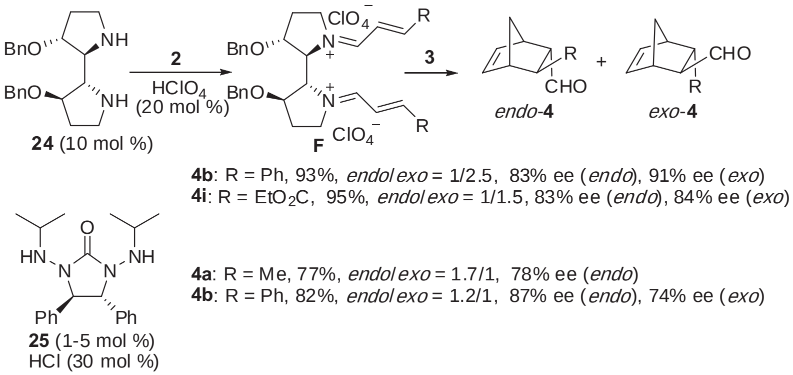
4a: R = Me, 72%, *endo*/*exo* < 1/20
88% ee (*exo*)
4b: R = Ph, 80%, *endo*/*exo* = 1/13
91% ee (*endo*), 92% ee (*exo*)
4i: R = EtO_2C, 90%, *endo*/*exo* = 1/5.5
56% ee (*endo*), 83% ee (*exo*)

Scheme 38.6 Chiral diamine salt catalyzed *exo*-selective Diels–Alder reactions.



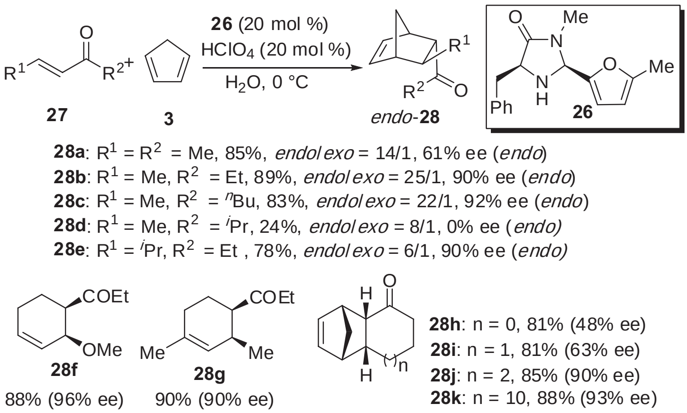
Scheme 38.7 Plausible mechanism for *exo*-selective Diels–Alder reactions.

Regarding the importance of iminium ion formation and geometry in organocatalytic Diels–Alder reactions, Zhang and coworkers designed and developed a new class of bipyrrolidines **24** as efficient organocatalysts that can form di-iminium intermediates **F** with α,β-unsaturated aldehydes [14]. The predominant *exo*-products were obtained with excellent enantioselectivities (Scheme 38.8). Recently, the Suzuki group reported a class of diamine catalysts (**25**) derived from hydrazines for this reaction to afford products **4** with a preference for the *endo* isomer (Scheme 38.8) [15].


BnO
NH
BnO
NH
24 (10 mol %)
2
HClO4 (20 mol %)
BnO
N+
ClO4⁻
R
BnO
N+
R
F ClO4⁻
3
R
CHO
endo-4
+
CHO
R
exo-4
4b: R = Ph, 93%, endo/exo = 1/2.5, 83% ee (endo), 91% ee (exo)
4i: R = EtO2C, 95%, endo/exo = 1/1.5, 83% ee (endo), 84% ee (exo)
HN
N
O
N
NH
Ph
Ph
25 (1-5 mol %)
HCl (30 mol %)
4a: R = Me, 77%, endo/exo = 1.7/1, 78% ee (endo)
4b: R = Ph, 82%, endo/exo = 1.2/1, 87% ee (endo), 74% ee (exo)

Scheme 38.8 Chiral diamine catalyzed enantioselective Diels–Alder reactions.

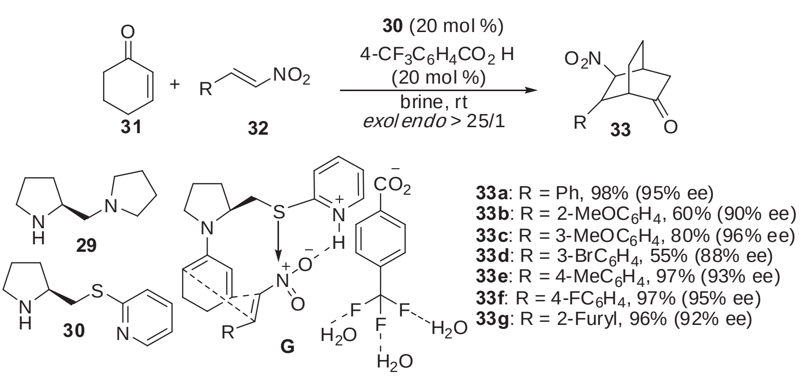
Most known chiral secondary-amine catalysts are effective only for less sterically hindered substrates such as α,β-unsaturated aldehydes. Asymmetric Diels–Alder reactions of acyclic α,β-unsaturated ketones represent a formidable challenge in this area. In 2002, MacMillan and coworkers accomplished the first general enantioselective Diels–Alder reactions of ketones by using chiral amine **26** [16]. As shown in Scheme 38.9, different substituents on **27** and cyclic or acyclic dienes were well tolerated in this transformation. The sense of asymmetric induction observed is consistent with selective approach of the diene substrate to the *Si*-face of the cis-iminium intermediate, which is further supported by computational models.


27
3
26 (20 mol %)
$HClO_4$ (20 mol %)
H_2O, 0 °C
endo-28
26
28a: $R^1 = R^2$ = Me, 85%, endo/exo = 14/1, 61% ee (endo)
28b: R^1 = Me, R^2 = Et, 89%, endo/exo = 25/1, 90% ee (endo)
28c: R^1 = Me, R^2 = ^{n}Bu, 83%, endo/exo = 22/1, 92% ee (endo)
28d: R^1 = Me, R^2 = ^{i}Pr, 24%, endo/exo = 8/1, 0% ee (endo)
28e: R^1 = ^{i}Pr, R^2 = Et , 78%, endo/exo = 6/1, 90% ee (endo)
28f
88% (96% ee)
28g
90% (90% ee)
28h: n = 0, 81% (48% ee)
28i: n = 1, 81% (63% ee)
28j: n = 2, 85% (90% ee)
28k: n = 10, 88% (93% ee)

Scheme 38.9 Enantioselective Diels–Alder reactions with α,β-unsaturated ketones.

38.2.1.1.2 **Enamine Activation**

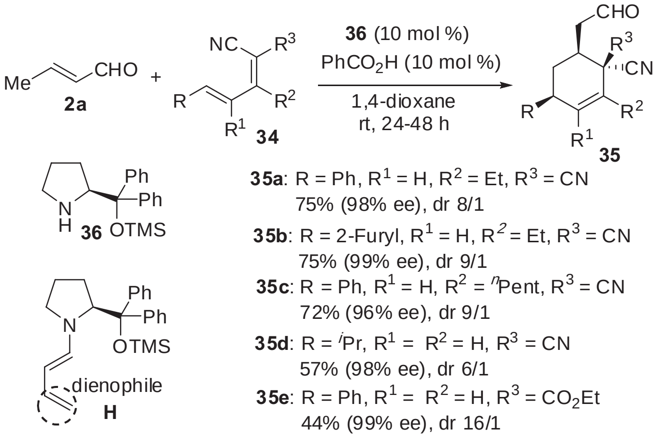
The first amine-catalyzed Diels–Alder reaction of α,β-unsaturated carbonyl compounds as dienes involving *in situ* enamine activation with chiral amine **29** through raising the diene HOMO energy was accomplished by Barbas and coworkers in 2002 with moderate enantioselectivity (up to 38% ee) [17a]. In 2007, Córdova and coworkers described chiral amine **29** catalyzed enantioselective Diels–Alder reactions between α,β-unsaturated cyclic ketones and nitroolefins with up to 86% ee [17b]. Two years later, Xu and coworkers successfully disclosed a highly efficient enantioselective Diels–Alder reaction of cyclohexenones **31** with aromatic nitroolefins **32** using amine **30** as catalyst in seawater or brine to give products **32** with excellent enantioselectivities (Scheme 38.10) [18a]. Notably, sea water and brine


31
32
30 (20 mol %)
4-$CF_3C_6H_4CO_2H$
(20 mol %)
brine, rt
exo/endo > 25/1
33
29
30
G
33a: R = Ph, 98% (95% ee)
33b: R = 2-$MeOC_6H_4$, 60% (90% ee)
33c: R = 3-$MeOC_6H_4$, 80% (96% ee)
33d: R = 3-BrC_6H_4, 55% (88% ee)
33e: R = 4-MeC_6H_4, 97% (93% ee)
33f: R = 4-FC_6H_4, 97% (95% ee)
33g: R = 2-Furyl, 96% (92% ee)

Scheme 38.10 Enamine activated enantioselective Diels–Alder reactions.

can significantly promote this reaction, possibly by stabilizing the transition state **G** via a hydrogen-bonding interaction with the acid **33** besides the salt effect. Recently, the same group has extended their study to supramolecular self-assemblies formed from chiral amines and poly(alkene glycol)s [18b].

Asymmetric inverse-electron-demand Diels–Alder reactions controlled by the dienophile HOMO and the diene LUMO have seldom been reported. Through a HOMO-activation strategy by the formation of dienamine intermediate **H** between crotonaldehyde (**2a**) and chiral amine **36** to raise the dienophile HOMO energy, Chen and coworkers successfully developed the first organocatalytic all-carbon-based inverse-electron-demand Diels–Alder reaction to produce multifunctional cycloadducts **35** with up to 99% ee (Scheme 38.11) [19].



35a: R = Ph, R^1 = H, R^2 = Et, R^3 = CN
75% (98% ee), dr 8/1

35b: R = 2-Furyl, R^1 = H, R^2 = Et, R^3 = CN
75% (99% ee), dr 9/1

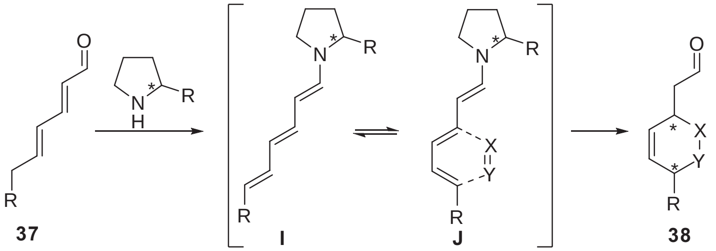
35c: R = Ph, R^1 = H, R^2 = ^{n}Pent, R^3 = CN
72% (96% ee), dr 9/1

35d: R = ^{i}Pr, R^1 = R^2 = H, R^3 = CN
57% (98% ee), dr 6/1

35e: R = Ph, R^1 = R^2 = H, R^3 = CO_2Et
44% (99% ee), dr 16/1

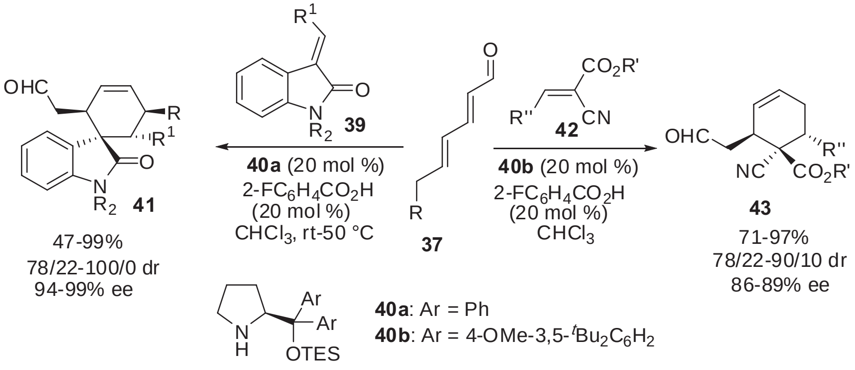
Scheme 38.11 Dienamine catalysis of Diels–Alder reactions.

Recently, Chen, Jørgensen, and coworkers discovered a novel activation mode by the condensation of chiral amines with polyenals **37** to generate reactive trienamine intermediates **J** that can participate in asymmetric Diels–Alder reactions with different classes of dienophiles (Scheme 38.12) to afford cycloadducts **38** [20]. With the use of chiral diarylprolinol silyl ether **40** as organocatalysts, various spirocyclic oxindoles **41** and multifunctional cyclohexenes **43** can be obtained in high



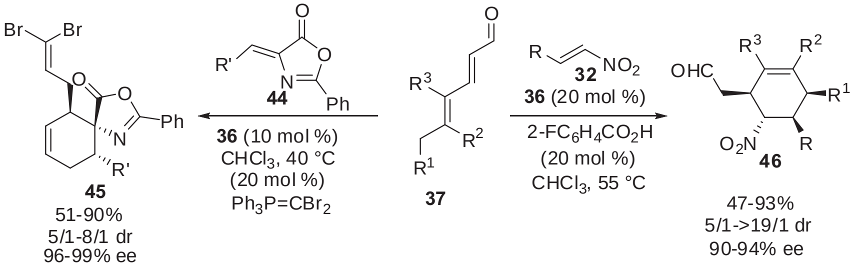
Scheme 38.12 Strategy for trienamine catalysis of Diels–Alder reactions.

yields with excellent regio- and stereoselectivities (Scheme 38.13). The amazing character of this activation strategy lies within the perfect chiral relay over a long distance of up to eight bonds.



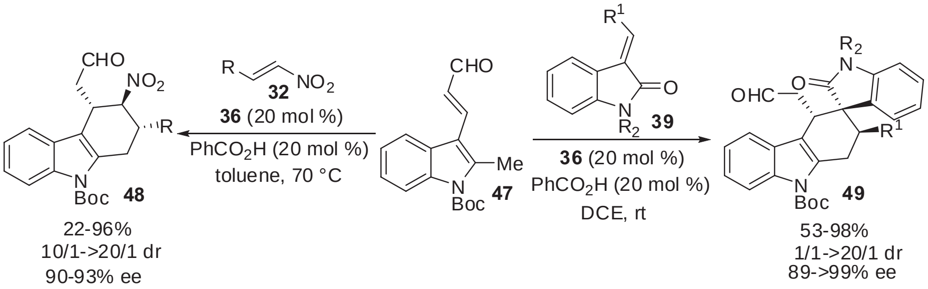
Scheme 38.13 Trienamine catalysis of enantioselective Diels–Alder reactions.

By means of trienamine catalysis of Diels–Alder reactions between polyenals **37** and olefinic azlactones **44**, Jørgensen and coworkers successfully uncovered a facile route to structurally rigid carbacyclic α,α-disubstituted amino acids derivatives **45** (Scheme 38.14) [21]. The above-mentioned trienamine catalysis is limited to highly activated dienophiles. To realize the Diels–Alder reactions of less reactive nitroolefins **32**, the Chen group adopted the strategy of introducing electron-donating alkyl substituents on polyenals **37** to further raise the HOMO energy. This strategy proved to be successful since various desired cycloadducts **46** can be obtained efficiently while unsubstituted 2,4-hexadienal and 2,4-heptadienal were inactive under the same conditions (Scheme 38.14) [22].



Scheme 38.14 Trienamine catalysis of enantioselective Diels–Alder reactions.

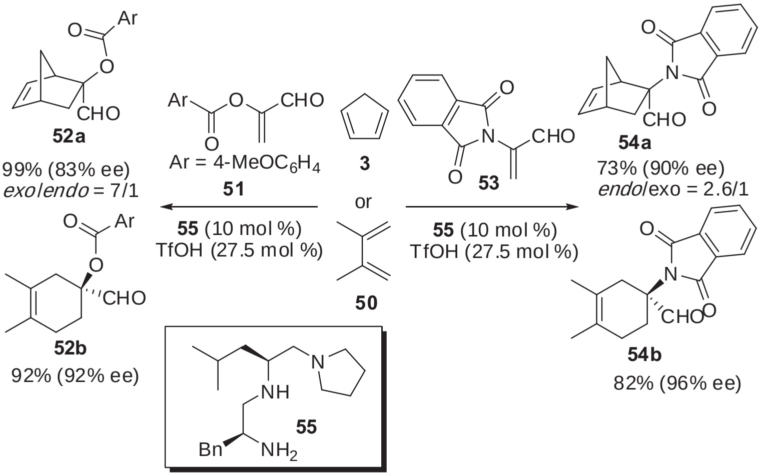
Although heterocyclic *ortho*-quinodimethanes (*o*QDMS) have been studied extensively to design Diels–Alder reactions for the synthesis of complex indole alkaloids for more than 30 years, asymmetric catalysis of the Diels–Alder reaction of nitroolefins **32** or methylene-indolinones **39** with *in situ* generated heterocyclic *o*QDMS from **47** and amine **36** has been achieved only recently by Melchiorre and coworkers (Scheme 38.15) [23]. This approach provides a straightforward route to optically active polycyclic heteroaromatic compounds with high diversity that would be difficult to synthesize by other methods.



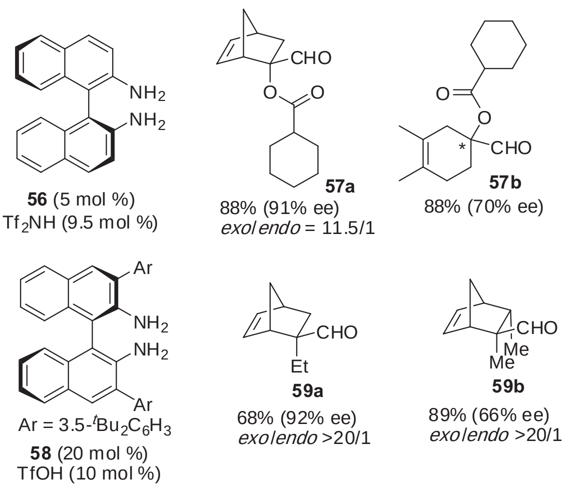
Scheme 38.15 Reactions with *in situ* generated heterocyclic *ortho*-quinodimethanes.

38.2.1.2 Chiral Primary Amine

In comparison with the widespread application of chiral secondary amines in organocatalytic Diels–Alder reactions, only a few successful examples have been reported with the use of chiral primary amines. In the case of α-substituted acroleins, it is difficult for chiral secondary amines to activate this type of substrates, probably because of poor generation of the corresponding iminium ions. To solve this problem, Ishihara and Nakano designed and synthesized a novel class of primary amine catalysts (**55**) [24]. Indeed, this type of less bulky ligand proved to be effective for enantioselective Diels–Alder reactions of α-acyloxyacroleins **51** or α-phthalimidoacroleins **53** to produce the desired cycloadducts **52** or **54** with quaternary stereocenters (Scheme 38.16).



Scheme 38.16 Triamine catalysis of Diels–Alder reactions.



56 (5 mol %)
Tf_2NH (9.5 mol %)

57a
88% (91% ee)
exo/*endo* = 11.5/1

57b
88% (70% ee)

Ar = 3.5-$^t Bu_2C_6H_3$
58 (20 mol %)
TfOH (10 mol %)

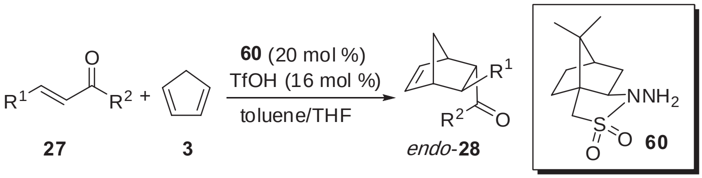
59a
68% (92% ee)
exo/*endo* >20/1

59b
89% (66% ee)
exo/*endo* >20/1

Figure 38.2 Binaphthyl-based diamine catalysts for Diels–Alder reactions α-substituted acroleins (Scheme 38.16).

To further improve the catalytic activity and enantioselectivity of primary amine catalyzed Diels–Alder reactions of α-substituted acroleins, the same group developed a binaphthyl-based diamine (**56**) containing relatively weak basic aromatic-amino groups. A diammonium salt of diamine **56** and the strong Brønsted acid Tf_2NH exhibited high activity and selectivity for the Diels–Alder reaction of α-acyloxyacroleins (Figure 38.2) [25]. In 2009, Maruoka and coworkers also disclosed an asymmetric Diels–Alder reaction of α-substituted α,β-unsaturated aldehydes using diamine **58** in combination with TfOH as organocatalyst to furnish the corresponding cycloadducts **59** containing all-carbon quaternary stereocenters (Figure 38.2) [26].

For chiral amine-catalyzed Diels–Alder reactions, α,β-unsaturated ketones are a challenging class of dienophiles. With the use of a primary camphor sulfonyl hydrazine **60** as organocatalyst, Lee and coworkers successfully realized asymmetric Diels–Alder reactions of α,β-unsaturated ketones **27** (Scheme 38.17) [27].



27 **3** *endo*-**28** **60**

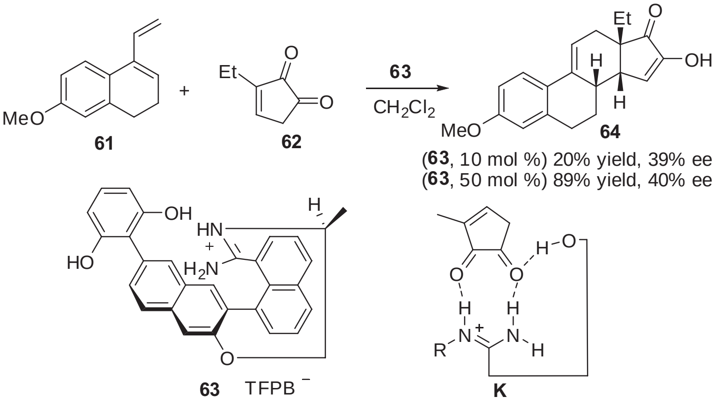
28l: R^1 = 4-$MeOC_6H_4$, R^2 = Me, 89% (96% ee), *endo*/*exo* = 24/1
28m: R^1 = 4-BrC_6H_4, R^2 = Me, 96% (92% ee), *endo*/*exo* = 24/1
28n: R^1 = 3-BrC_6H_4, R^2 = Me, 82% (84% ee), *endo*/*exo* = 24/1
28o: R^1 = 2-BrC_6H_4, R^2 = Me, 85% (11% ee), *endo*/*exo* = 5.7/1
28p: R^1 = 4-$MeOC_6H_4$, R^2 = Ph, 70% (84% ee), *endo*/*exo* = 24/1

Scheme 38.17 Camphor sulfonyl hydrazine catalyzed Diels–Alder reactions.

The key iminium intermediate of the catalytic cycle was isolated. When it was put back into the reaction system, the same level of reactivity and selectivity was observed.

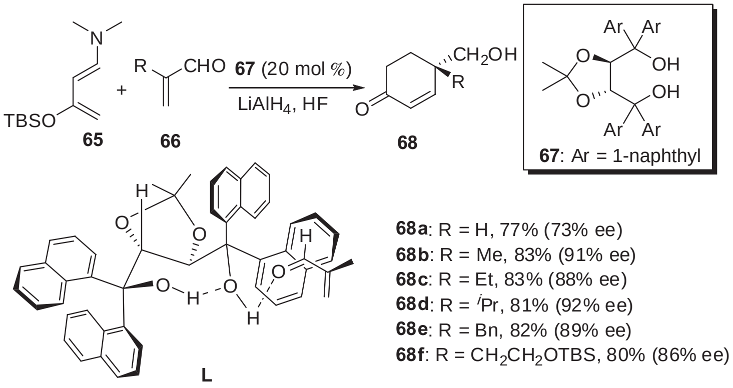
38.2.2
Chiral Brønsted Acids Catalysts (Hydrogen-Bonding or Brønsted Acid Activation)

Accelerating Diels–Alder reactions by the use of hydrogen bonding to activate the dienophile reaction has been long recognized. However, the first hydrogen-bonding promoted enantioselective Diels–Alder reaction was not reported until 2000, by Göbel and coworkers [28]. Axially chiral amidinium ion **63** activated dienophile **62** through double hydrogen bonds (model **K**) to give only 40% ee with as high as 50 mol% of catalyst loading (Scheme 38.18). Later, the same group developed a C_2-chiral bis(amidinium) catalyst for this reaction, which still led to a low enantioselectivity [29].


MeO
61
+
Et
O
O
62
63
CH2Cl2
Et
O
H
OH
H
MeO
64
(63, 10 mol %) 20% yield, 39% ee
(63, 50 mol %) 89% yield, 40% ee
OH
HO
HN
+
H2N
H
O
63 TFPB⁻
O
O
H
H
O
H
R
N
+
N
H
K

Scheme 38.18 Hydrogen-bonding promoted Diels–Alder reactions.

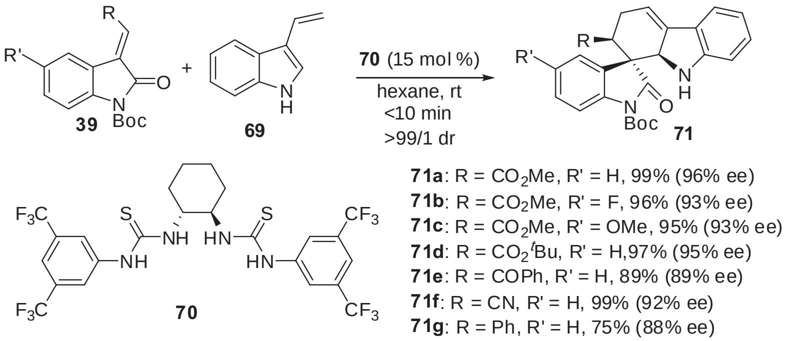
With the use of TADDOL **67** as catalyst, Rawal and coworkers described the first highly enantioselective Diels–Alder reaction of aminosiloxydienes **65** with substituted acroleins **66** [30]. Different substituents on acroleins were well tolerated to give the desired products **68** in high yields with excellent enantioselectivities (Scheme 38.19). As shown in the asymmetric induction model **L**, it was supposed that the dienophile was activated by intermolecular hydrogen bonding between carbonyl and hydroxyl groups, and the intramolecular hydrogen bonding between two hydroxyl groups of the TADDOL catalyst can facilitate the intermolecular hydrogen-bonding activation for catalysis.



68a: R = H, 77% (73% ee)
68b: R = Me, 83% (91% ee)
68c: R = Et, 83% (88% ee)
68d: R = ^{i}Pr, 81% (92% ee)
68e: R = Bn, 82% (89% ee)
68f: R = CH_2CH_2OTBS, 80% (86% ee)

Scheme 38.19 Hydrogen-bonding catalyzed enantioselective Diels–Alder reactions.

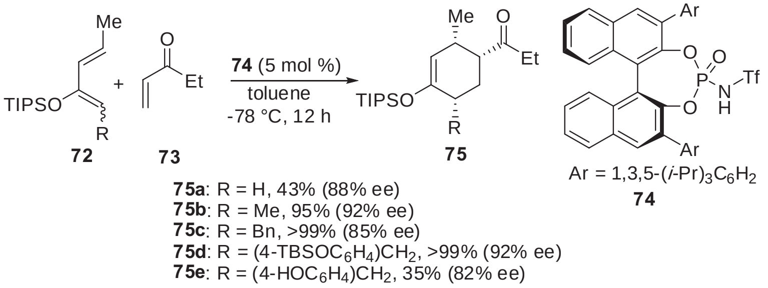
Hydrogen-bonding catalysis of the Diels–Alder reaction of 2-vinylindoles **39** and methylene-indolinones **69** has been accomplished by the Barbas group using a C_2-symmetric bis-thiourea organocatalyst [31]. This efficient transformation provided a powerful approach by which to construct carbazole-spirooxindole derivatives **71** extremely rapidly (less than 10 min) with excellent enantiopurity and structure diversity (Scheme 38.20).



71a: R = CO_2Me, R' = H, 99% (96% ee)
71b: R = CO_2Me, R' = F, 96% (93% ee)
71c: R = CO_2Me, R' = OMe, 95% (93% ee)
71d: R = $CO_2{}^tBu$, R' = H,97% (95% ee)
71e: R = COPh, R' = H, 89% (89% ee)
71f: R = CN, R' = H, 99% (92% ee)
71g: R = Ph, R' = H, 75% (88% ee)

Scheme 38.20 Chiral thiourea catalyzed enantioselective Diels–Alder reactions.

The utility of weak-acidic Brønsted acid catalysts for the Diels–Alder reaction is often limited to reactive substrates. To overcome this drawback, Yamamoto and coworkers designed chiral *N*-triflyl phosphoramide **74** with higher acidity as catalyst for the enantioselective Diels–Alder reaction of ethyl vinyl ketone (**73**) with electron-rich silyloxydiene **72** [32]. Various multifunctional cyclohexenes **75** can be obtained in moderate to excellent yields with high enantioselectivities (Scheme 38.21).

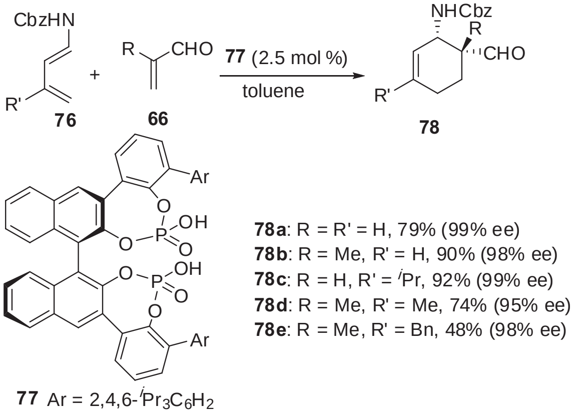


Ar = 1,3,5-(i-Pr)$_3$C$_6$H$_2$
74

75a: R = H, 43% (88% ee)
75b: R = Me, 95% (92% ee)
75c: R = Bn, >99% (85% ee)
75d: R = (4-TBSOC$_6$H$_4$)CH$_2$, >99% (92% ee)
75e: R = (4-HOC$_6$H$_4$)CH$_2$, 35% (82% ee)

Scheme 38.21 Chiral phosphoramide catalyzed enantioselective Diels–Alder reactions.

Recently, chiral bis-phosphoric acid **77** bearing a new chiral scaffold with triple axial chirality assisted by intramolecular hydrogen-bonding between two phosphoric acid moieties was designed as a new chiral Brønsted acid catalyst by the Terada group [33]. Application of this catalyst in the Diels–Alder reaction between substituted acroleins **66** and amido-dienes **76** produced the corresponding cycloadducts **78** with excellent enantioselectivities (Scheme 38.22). In comparison with the mono-phosphoric acid, bis-phosphoric acid **77** showed obviously higher catalytic activity and selectivity.



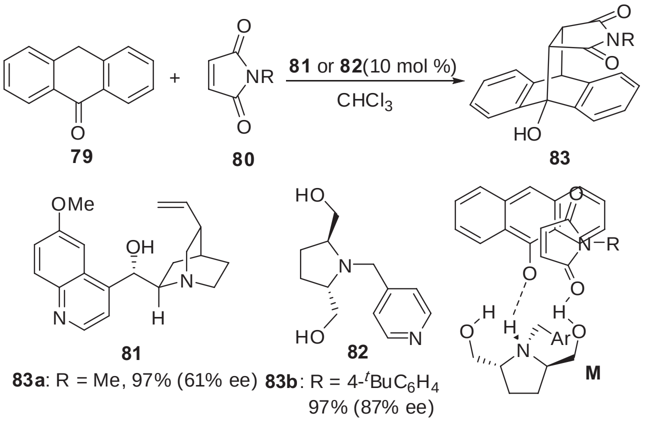
77 Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$

78a: R = R' = H, 79% (99% ee)
78b: R = Me, R' = H, 90% (98% ee)
78c: R = H, R' = ^{i}Pr, 92% (99% ee)
78d: R = Me, R' = Me, 74% (95% ee)
78e: R = Me, R' = Bn, 48% (98% ee)

Scheme 38.22 Chiral bis-phosphoric acid catalyzed Diels–Alder reactions.

38.2.3
Chiral Bifunctional Catalysts

The first asymmetric chiral-base catalyzed Diels–Alder reaction of anthrone **79** with maleimide **80** was achieved by Kagan and Riant in 1989 [4]. With the use of quinidine (**81**) as catalyst, the cycloadduct **83a** can be obtained in 97% yield with 61% ee (Scheme 38.23). The enantioselectivity was further improved to 87% by

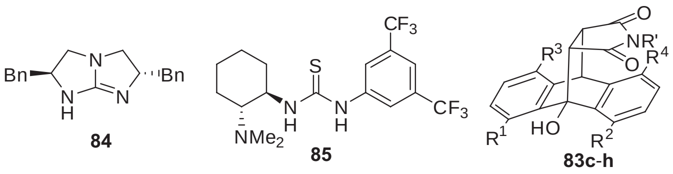


83a: R = Me, 97% (61% ee) **83b**: R = 4-^{t}BuC$_6$H$_4$ 97% (87% ee)

Scheme 38.23 Chiral base catalyzed asymmetric Diels–Alder reactions.

the Yamamoto group using chiral pyrrolidine **82** as bifunctional catalyst (Scheme 38.23) [34]. As shown in the proposed transition state model **M**, two hydrogen bonds are believed to exist, one is between the protonated pyrrolidine catalyst **82** and anthrone enolate and the other is between hydroxyl group of pyrrolidine and carbonyl group of maleimide **80**. Such a double hydrogen-bonding interaction ensures that substrate activation and stereochemistry control occur simultaneously.

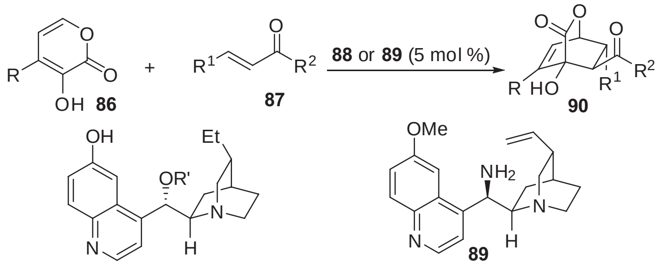
More recently, Tan and coworkers successfully broadened the substrate scope and improved the enantioselectivities for the Diels–Alder reactions of anthrones by utilizing new chiral bicyclic guanidine **84** as catalyst (Figure 38.3) [35]. Notably,



84 (10 mol %) as catalyst
- **83c**: R^1 = R^2 = R^3 = R^4 = H, R' = 2-NO$_2$C$_6$H$_4$, 87% (98% ee)
- **83d**: R^1 = R^2 = Cl, R^3 = R^4 = H, R' = Bn, 92% (95% ee)
- **83e**: R^1 = R^2 = H, R^3 = R^4 = Cl, R' = Ph, 92% (99% ee)
- **83f**: R^1 = R^4 = H, R^2 = R^3 = Cl, R' =Ph, 87% (99% ee)
- **83g**: R^1 = R^2 = R^4 = H, R^3= NHMe, R = Et, 95% (98% ee)

85 (10 mol %) as catalyst
- **83h**: R^1 = R^2 = R^3 = R^4 = H, R = Ph, R = Et, 100% conv (90% ee)

Figure 38.3 Chiral guanidine or thiourea catalysts for Diels–Alder reactions of anthrones (Scheme 38.23).



88 R' = 9-phenanthrenyl

with 20 mol % TFA

90a: R = H, R^1 = Ph, R^2 = CO_2Et
87% (94% ee), *exo*/*endo* = 13/1
90b: R = H, R^1 = Ph, R^2 = COPh
100% (90% ee), *exo*/*endo* = 13/1
90c: R = Ph, R^1 = Ph, R^2 = CO_2Et
84% (85% ee), *exo*/*endo* = 19/1
90d: R = Br, R^1 = Ph, R^2 = CO_2Et
75% (83% ee), *exo*/*endo* = 5.7/1

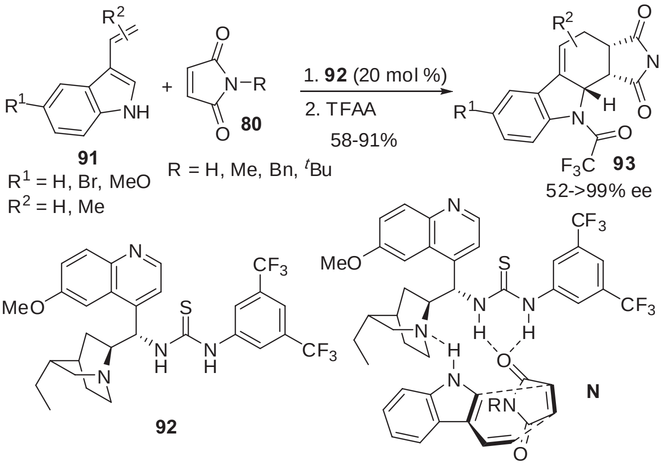
90e: R = H, R^1 = Ph, R^2 = Me
87% (98% ee), *exo*/*endo* = 4/1
90f: R = H, R^1 = 2-Thenyl, R^2 = Me
85% (99% ee), *exo*/*endo* = 4/1
90g: R = H, R^1 = H, R^2 = Et
99% (99% ee), *exo*/*endo* = 32/1
90h: R = Ph, R^1 = Ph, R^2 = Me
83% (96% ee), *exo*/*endo* = 5/1

Scheme 38.24 Asymmetric Diels–Alder reactions of 2-pyrones.

prolonged reaction time or the treatment of the isolated cycloadducts under basic condition can cause a retro-aldol ring-opening reaction. Bifunctional thiourea catalyst **85** was also effective for the organocatalytic Diels–Alder reaction of anthrones **80**, through the urea moiety to activate the maleimide and the tertiary amine to deprotonate the anthrone (Figure 38.3) [36].

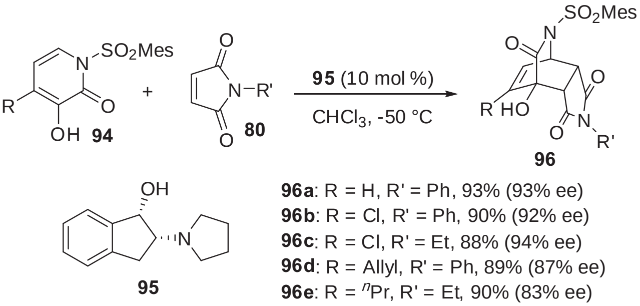
An alternative organocatalytic Diels–Alder reaction of 2-pyrones **86** with α,β-unsaturated ketones or esters **87** was developed by the Deng group with the use of bifunctional cinchona alkaloids catalysts **88** to afford the corresponding adducts **90** in high yields with excellent stereoselectivities (Scheme 38.24) [37]. Both hydrogen bond donor and acceptor moieties are involved in catalyst **88**, which provides the possibility of multiple hydrogen bonding interaction between catalyst and substrates to raise the diene HOMO energy and lower the dienophile LUMO energy. The dienophile scope can be also extended to conjugated nitriles when using cinchona-based thiourea as catalyst [37]. Later, the same group disclosed the class of highly effective 9-NH_2 cinchona alkaloids catalyst **89** for this type of Diels–Alder reaction with a broad substrate scope (Scheme 38.24) [38]. Catalyst **89** was presumed to possess the ability to simultaneous activate diene and dienophile with its primary amine and quinuclidine motifs, respectively.

In 2008, the first asymmetric Diels–Alder reaction of 3-vinylindoles **91** and maleimides **80** with a bifunctional thiourea catalyst (**92**) was realized by Bernardi and coworkers (Scheme 38.25) [39]. The resultant highly-enantioenriched fused heterocycles are very useful for the synthesis of biologically important natural or unnatural alkaloids. As shown in the proposed transition state **N**, catalyst **92** probably activates the diene with the basic moiety and activates the dienophile with the thiourea moiety through hydrogen bonding interactions.



Scheme 38.25 Asymmetric Diels–Alder reactions of 3-vinylindoles.

The reported organic bifunctional catalysts possessing both hydrogen bond donor and acceptor moieties are often derived from the cinchona alkaloids. Tan and coworkers developed the simple and readily available amino-indanol **95** as an efficient bifunctional organocatalyst for the enantioselective Diels–Alder reaction of 3-hydroxy-2-pyridones **94** (Scheme 38.26) [40]. Besides maleimides **80**, alkyl vinyl ketones were also suitable dienophiles for this catalytic system.


94
80
95 (10 mol %)
CHCl₃, -50 °C
96
95
96a: R = H, R' = Ph, 93% (93% ee)
96b: R = Cl, R' = Ph, 90% (92% ee)
96c: R = Cl, R' = Et, 88% (94% ee)
96d: R = Allyl, R' = Ph, 89% (87% ee)
96e: R = ⁿPr, R' = Et, 90% (83% ee)

Scheme 38.26 Asymmetric Diels–Alder reactions of 2-pyridones.

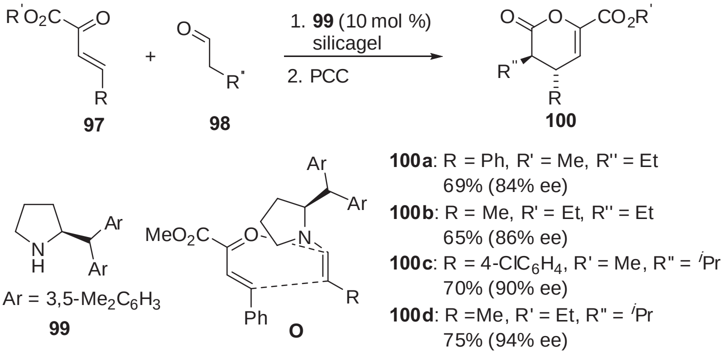
38.3
Organocatalysis of Oxa-Hetero-Diels–Alder Reaction

The asymmetric hetero-Diels–Alder reaction involving carbonyl compounds as the heterodienophiles or heterodienes is among the most powerful methodologies for the construction of enantioenriched oxygen-containing heterocycles that have wide synthetic applications in biologically important natural or unnatural molecules.

For a long period, chiral Lewis acids were the most studied catalysts. Only recently have chiral bases, Brønsted acids, and N-heterocyclic carbenes been utilized as effective organocatalysts for the oxa-hetero-Diels–Alder reaction.

38.3.1
Chiral Bases as Catalysts

In 2003, the first organocatalytic enantioselective inverse-electron-demand hetero-Diels–Alder reaction of β,γ-unsaturated-α-ketones **97** with aldehydes **98** promoted by a secondary amine catalyst (**99**) was accomplished by the Jørgensen group [41]. After oxidation by pyridinium chlorochromate (PCC), various *trans*-lactones **100** were afforded with good yields and up to 94% ee (Scheme 38.27). The reaction is proposed to occur via an enamine intermediate generated from chiral secondary amine **99** and aldehydes **98** (transition state **O**). Notably, silica gel is essential for regeneration of the chiral amine catalyst.



100a: R = Ph, R' = Me, R'' = Et
69% (84% ee)
100b: R = Me, R' = Et, R'' = Et
65% (86% ee)
100c: R = 4-ClC$_6$H$_4$, R' = Me, R'' = ^{i}Pr
70% (90% ee)
100d: R =Me, R' = Et, R'' = ^{i}Pr
75% (94% ee)

Scheme 38.27 Chiral amine catalyzed hetero-Diels–Alder reactions.

According to the above-mentioned strategy, Zhao and coworkers successfully extended the diene scope to β,γ-unsaturated-α-ketophosphonates with the use of proline-derived catalyst **101** [42]. The corresponding cycloadducts **102** were obtained with up to 94% ee (Figure 38.4). Subsequently, Liu and coworkers reported a similar reaction with α,β-unsaturated trifluoromethyl ketones as dienes under the catalysis of secondary amine **36** to give optically active fluoro-containing lactone derivatives **103** (Figure 38.4) [43].

An enantioselective inverse-electron-demand hetero-Diels–Alder reaction of *o*-quinones **104** and aldehydes **98** was disclosed by the Dixon group with the use of secondary amine catalyst **105** [44]. This reaction went smoothly through *in situ* generated enamines with *o*-quinone reagents to afford the corresponding products **106** (with up to 81% ee), which can be further converted into optically active 2,3-dihydro-benzo[1,4]dioxin compounds (Scheme 38.28).

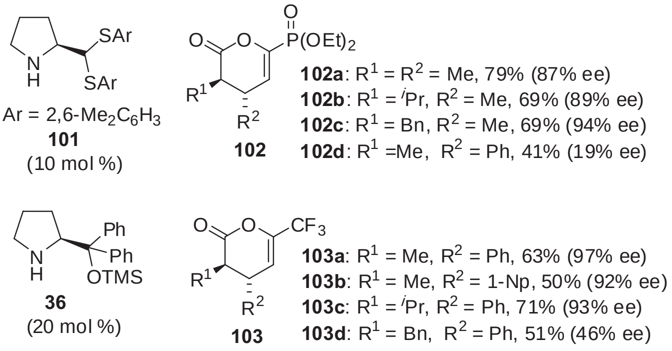
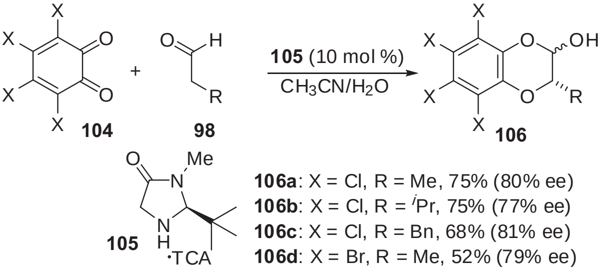
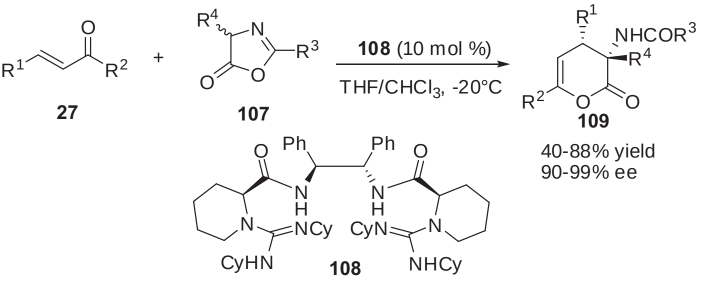

SAr
SAr
N
H
Ar = 2,6-Me2C6H3
101
(10 mol %)
O
P(OEt)2
R1
R2
102
102a: R1 = R2 = Me, 79% (87% ee)
102b: R1 = iPr, R2 = Me, 69% (89% ee)
102c: R1 = Bn, R2 = Me, 69% (94% ee)
102d: R1 =Me, R2 = Ph, 41% (19% ee)
Ph
Ph
OTMS
36
(20 mol %)
CF3
103
103a: R1 = Me, R2 = Ph, 63% (97% ee)
103b: R1 = Me, R2 = 1-Np, 50% (92% ee)
103c: R1 = iPr, R2 = Ph, 71% (93% ee)
103d: R1 = Bn, R2 = Ph, 51% (46% ee)

Figure 38.4 Products of amine-catalyzed inverse-electron-demand hetero-Diels–Alder reactions.


X
O
104
H
R
98
105 (10 mol %)
CH3CN/H2O
OH
R
106
Me
105
·TCA
106a: X = Cl, R = Me, 75% (80% ee)
106b: X = Cl, R = iPr, 75% (77% ee)
106c: X = Cl, R = Bn, 68% (81% ee)
106d: X = Br, R = Me, 52% (79% ee)

Scheme 38.28 Asymmetric inverse-electron-demand hetero-Diels–Alder reactions of *o*-quinones.

Recently, Feng and coworkers designed a new class of C_2-symmetric chiral bisguanidine (**108**) as a highly efficient organocatalyst to accomplish the first asymmetric inverse-electron-demand hetero-Diels–Alder reaction of chalcones **27** with racemic azlactones **107** [45]. A broad range of chalcones and azlactones were suitable for this transformation, affording lactone derivatives **109** containing α-quaternary-β-tertiary stereocenters with excellent enantioselectivities as major products along with small amount of Michael adducts (Scheme 38.29). Hydrogen

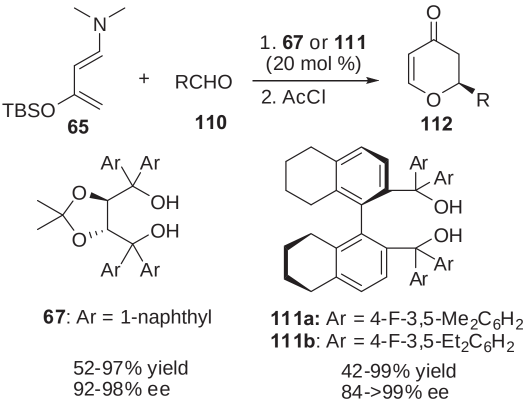


Scheme 38.29 Chiral guanidine catalyzed hetero-Diels–Alder reactions.

bonds were considered to be crucial for the activation and stereoinduction of the reaction.

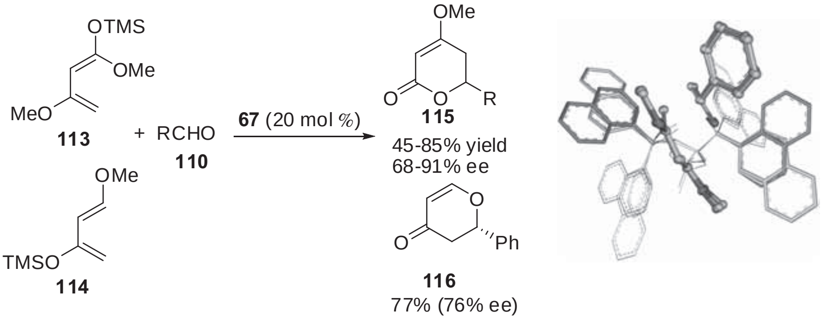
38.3.2
Chiral Brønsted Acids as Catalysts

Chiral Brønsted acids usually activate oxa-hetero-Diels–Alder through the hydrogen bonding interaction between the catalyst and the dienophile. Although hydrogen bonding is widely present in nature, using this weak interaction to promote enantioselective hetero-Diels–Alder reactions is only a recent event. In 2003, the Rawal group achieved the first highly enantioselective hetero-Diels–Alder reaction of aldehydes (**110**) with electron-rich 1,3-diene **65** with the use of TADDOL **67** as an efficient catalyst through hydrogen bonding activation [46]. After treatment with acetyl chloride, various dihydropyranones **112** were obtained in high yields with excellent enantioselectivities (Scheme 38.30). Later, Rawal, Yamamoto, and coworkers developed an alternative chiral Brønsted acid catalyst (**111**) containing a partly reduced chiral binaphthyl skeleton, which showed high catalytic activity and enantioselectivity for the same transformation (Scheme 38.30) [47, 48].



Scheme 38.30 Hydrogen-bonding catalyzed hetero-Diels–Alder Reactions.

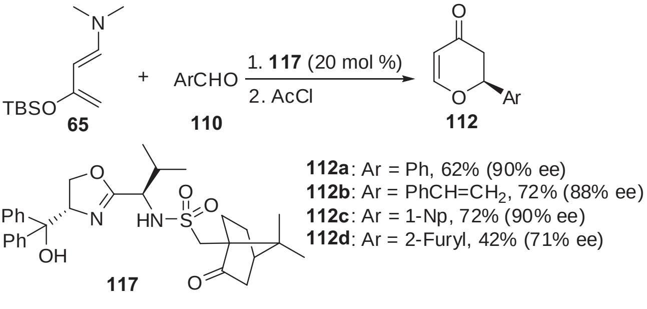
In 2004, Ding and coworkers developed the first catalytic enantioselective hetero-Diels–Alder reaction of Brassard's diene **113** with aldehydes **110** through hydrogen bonding activation using **67** as the catalyst to afford optically active δ-lactones in moderate-to-good yields with up to 91% ee (Scheme 38.31) [49]. Notably, (*S*)-(+)-dihydrokawain can be synthesized in one step from 3-phenylpropionaldehyde in 50% isolated yield and 69% ee by means of this methodology. Later, the same group found that TADDOL **67** can also catalyze the asymmetric hetero-Diels–Alder reaction of the less active Danishefsky's diene (**114**) [50].



Scheme 38.31 TADDOL-catalyzed hetero-Diels–Alder reactions.

On the basis of the X-ray crystal structures of TADDOL–DMF and **111**–benzaldehyde complexes [47, 50], and computational studies, the hydrogen bonding interaction model and asymmetric induction pathway were then systematically investigated by Ding and Wu [50]. In agreement with the experimental findings, the calculations indicate that this TADDOL-catalyzed hetero-Diels–Alder reaction proceeds via a concerted mechanism through an asynchronous and zwitterionic transition structure. The carbonyl group of benzaldehyde is activated by forming an intermolecular hydrogen bond with one of the hydroxyl groups of TADDOL. Meanwhile, the intramolecular hydrogen bond between the two hydroxyl groups in TADDOL is found to facilitate the intermolecular hydrogen bonding with benzaldehyde [50].

The Sigman group designed a novel hydrogen-bond catalyst (**117**) containing a chiral oxazoline backbone for the enantioselective hetero-Diels–Alder reaction of amino-diene **65** with aldehydes **110** (Scheme 38.32) [51a]. Both hydrogen bonds in **117** are found to be crucial for effective catalysis. Further systematic studies on the effect of catalyst acidity by the same group indicate that greater catalyst acidity leads to increased activity and enantioselectivity [51b,c].

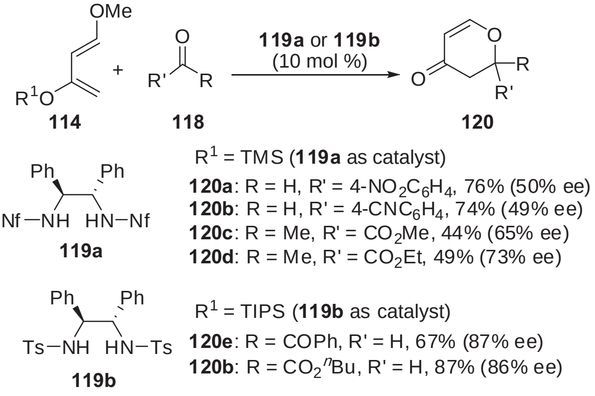


112a: Ar = Ph, 62% (90% ee)
112b: Ar = PhCH=CH$_2$, 72% (88% ee)
112c: Ar = 1-Np, 72% (90% ee)
112d: Ar = 2-Furyl, 42% (71% ee)

Scheme 38.32 Hydrogen-bond catalyzed hetero-Diels–Alder reactions.

In 2005, Jørgensen and Mikami independently reported the hetero-Diels–Alder reaction of Danishefsky's diene **114** with glyoxylates or glyoxals **118** using a class of chiral bis-sulfonamides catalyst **119a,b** derived from 1,2-diphenyl-1,2-diamine

[52, 53]. Through the double hydrogen bonding catalysis, the desired cycloadducts **120** were obtained in moderate to good yields with up to 87% ee (Scheme 38.33). Moreover, in recent years, a few hydrogen-bonding catalysts have also been developed for the oxa-hetero-Diels–Alder reaction [54].



114 **118** **120**

119a

R^1 = TMS (**119a** as catalyst)

120a: R = H, R' = 4-$NO_2C_6H_4$, 76% (50% ee)
120b: R = H, R' = 4-CNC_6H_4, 74% (49% ee)
120c: R = Me, R' = CO_2Me, 44% (65% ee)
120d: R = Me, R' = CO_2Et, 49% (73% ee)

119b

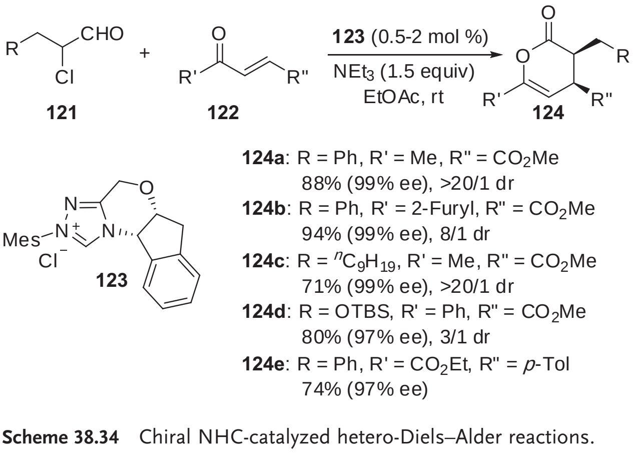
R^1 = TIPS (**119b** as catalyst)

120e: R = COPh, R' = H, 67% (87% ee)
120b: R = $CO_2{}^nBu$, R' = H, 87% (86% ee)

Scheme 38.33 Hydrogen-bond catalyzed hetero-Diels–Alder reactions.

38.3.3
Chiral *N*-Heterocyclic Carbenes as Catalysts

Chiral N-heterocyclic carbenes (NHCs) can serve as a new class of organocatalysts for the enantioselective inverse-electron-demand hetero-Diels–Alder reaction though the catalytic generation of a chiral enolate that acts as a highly reactive dienophile. In 2006, Bode and coworkers disclosed the first highly enantioselective oxa-hetero-Diels–Alder reaction of racemic α-chloroaldehydes **121** catalyzed by a N-heterocyclic carbene generated from *N*-substituted azolium salt **123** in the presence of triethylamine [55]. With 0.5–2.0 mol% catalyst, various synthetically valuable products **124** can be obtained in excellent yields and stereoselectivities (Scheme 38.34). The observed very high cis diastereoselectivities were postulated



121 **122** **124**

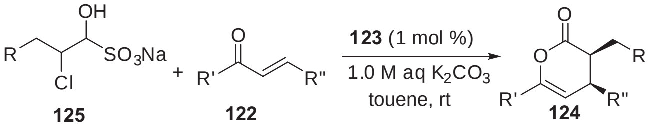
123

124a: R = Ph, R' = Me, R'' = CO_2Me
88% (99% ee), >20/1 dr
124b: R = Ph, R' = 2-Furyl, R'' = CO_2Me
94% (99% ee), 8/1 dr
124c: R = $^nC_9H_{19}$, R' = Me, R'' = CO_2Me
71% (99% ee), >20/1 dr
124d: R = OTBS, R' = Ph, R'' = CO_2Me
80% (97% ee), 3/1 dr
124e: R = Ph, R' = CO_2Et, R'' = *p*-Tol
74% (97% ee)

Scheme 38.34 Chiral NHC-catalyzed hetero-Diels–Alder reactions.

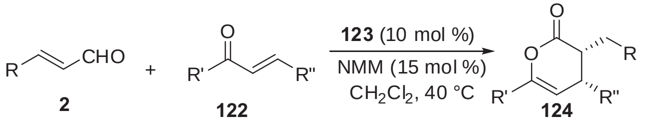
to arise from the stereoselective formation of (*Z*)-enolate in the redox reaction of enals in conjunction with a high preference for an *endo* cycloaddition.

To overcome the drawbacks of α-chloroaldehydes, such as sensitivity to moisture and oxygen and difficulties and lack of safety in obtaining the pure form, the Bode group employed easily available, bench-stable α-chloroaldehyde bisulfite adducts **125** as dienophile precursors in NHC-catalyzed hetero-Diels–Alder reactions under biphasic conditions to give cycloadducts **124** with high levels of enantioselectivity (Scheme 38.35) [56]. This reaction represents the first enantioselective NHC-catalyzed reaction that is demonstrably water-tolerant. Later, the Bode group further enlarged the dienophile scope to α,β-unsaturated aldehydes **2**, which can be converted into chiral ester enolate equivalents with chiral NHC precatalyst **123** as active dienophiles for the enantioselective hetero-Diels–Alder reaction (Scheme 38.36) [57]. The strength of the catalytic base used to generate the active N-heterocyclic carbene catalyst was found to be critical for successful enolate formation.



124f: R = H, R' = Ph, R'' = CO_2Et, 84% (90% ee)
124g: R = H, R' = CO_2Et, R'' = ^{n}Pr, 80% (>99% ee)
124h: R = Ph, R' = Ph, R'' = CO_2Et, 98% (99% ee)
124i: R = $^nC_9H_{19}$, R' = Ph, R'' = CO_2Et, 74% (>99% ee)
124j: R = Ph, R' = CO_2Et, R'' = ^{n}Pr, 78% (>99% ee)

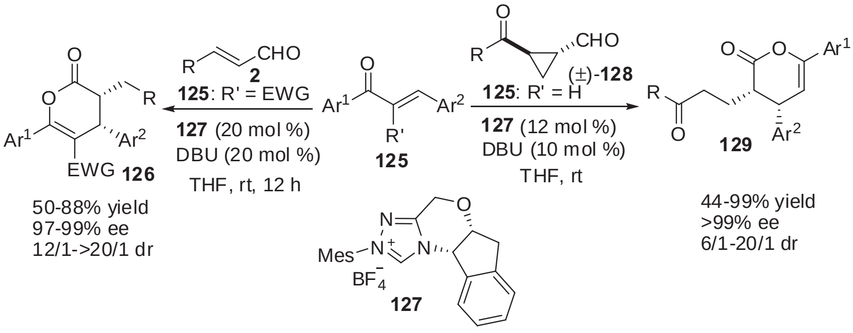
Scheme 38.35 Hetero-Diels–Alder reactions with α-chloroaldehyde bisulfite salts.



124k: R = Ph, R' = $Me_2(OH)C$, R'' = CO_2Et, 93% (99% ee), >20/1 dr
124l: R = 2-Furyl, R' = $Me_2(NHCbz)C$, R'' = CO_2Et, 98% (>99% ee), 20/1 dr
124m: R = H, R' = 4-$MeOC_6H_4$, R'' = CO_2Me, 54% (99% ee), >20/1 dr
124n: R = $^nC_3H_7$, R' = Me, R'' = CO_2Et, 95% (>94% ee), >20/1 dr
124o: R = Ph, R' = CO_2Et, R'' = Me, 85% (98% ee)

Scheme 38.36 Hetero-Diels–Alder reactions with α,β-unsaturated aldehydes.

Using a strong base such as DBU in Bode's catalytic system was found to lead to significant competing homoenolate pathway products. By the introduction of an electron-withdrawing group at the α-position of chalcones, Chi and coworkers successfully realized the N-heterocyclic carbene catalysis of the hetero-Diels–Alder reaction in the presence of DBU (Scheme 38.37) [58a]. No typical homoenolate pathway products were observed. Moreover, the Chi group also disclosed an NHC catalyzed (formal) hetero-Diels–Alder reaction between chalcones **125** and formylcyclopropanes **128** to produce optically pure multisubstituted cyclohexane derivatives **129** in high yields (Scheme 38.37) [58b].



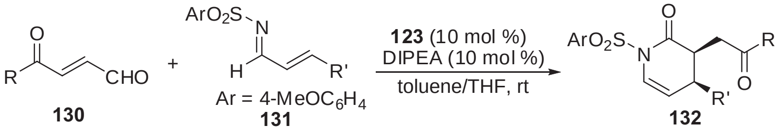
Scheme 38.37 NHC-catalyzed hetero-Diels–Alder reactions.

38.4
Organocatalysis of Aza-Hetero-Diels–Alder Reaction

The enantioselective aza-hetero-Diels–Alder reaction is one of the most convergent strategies for the synthesis of biologically and pharmaceutically important nitrogen-containing heterocycles. This importance has led to great efforts made on the asymmetric aza-hetero-Diels–Alder reaction. Several types of organocatalysts have been developed for this intriguing transformation.

38.4.1
Chiral Carbenes as Catalysts

In 2006, Bode and coworkers reported the first enantioselective inverse-electron-demand hetero-Diels–Alder reaction of enals **130** with α,β-unsaturated imines **131** under the catalysis of carbene precatalyst **123** in combination with Hünig's base [59]. A broad range of substrates were well tolerated to afford synthetically important dihydropyridinone products **132** in good yields with remarkable enantioselectivities (Scheme 38.38). The need to introduce electron-withdrawing groups for enals only lies within the increased electrophilicity of these substrates, which enhances the rate of their reaction with the nucleophilic catalysts. The observed



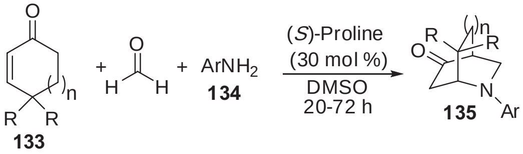
132a: R = OEt, R' = Ph, 90% (99% ee)
132b: R = OEt, R' = 4-AcC$_6$H$_4$, 55% (99% ee)
132c: R = OEt, R' = 2-Furyl, 71% (99% ee)
132d: R = OEt, R' = ^{n}Pr, 58% (99% ee)
132e: R =Me, R' = Ph, 51% (99% ee)
132f: R = Ph, R' = 4-MeOC$_6$H$_4$, 52% (99% ee)

Scheme 38.38 N-heterocyclic carbene catalyzed azadiene Diels–Alder reactions.

high cis diastereoselectivities were attributed to the stereoselective formation of (*Z*)-enolate and the preference for an *endo* cycloaddition.

38.4.2
Chiral Amines as Catalysts

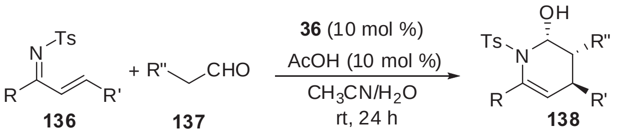
In 2005, Córdova and coworkers described the first example of the enantioselective organocatalytic aza-hetero-Diels–Alder reaction [60]. The one-pot three-component direct aza-hetero-Diels–Alder reaction under the catalysis of proline afforded the desired cycloadducts **135** with excellent chemo-, regio-, and stereoselectivity (Scheme 38.39). This reaction was considered to proceed via a plausible Mannich–Michael reaction pathway. Recently, Wang and coworkers developed a chiral ionic liquid catalyst for this reaction to afford up to >99% ee [61].

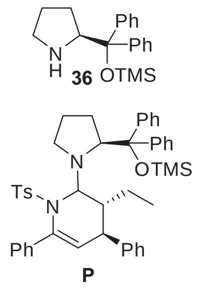


135a: R = H, Ar = 4-MeOC$_6$H$_4$, n = 1, 82% (99% ee)
135b: R = Me, Ar = 4-MeOC$_6$H$_4$, n = 1, 70% (>99% ee)
135c: R = H, Ar = 4-MeOC$_6$H$_4$, n = 2, 90% (98% ee)
135d: R = H, Ar = Ph, n = 1, 54% (>96% ee)

Scheme 38.39 Proline-catalyzed three component aza-hetero-Diels–Alder reactions.

Chen and coworkers presented a highly stereoselective inverse-electron-demand aza-hetero-Diels–Alder reaction of aldehydes **137** and α,β-unsaturated imines **136** with the use of a chiral secondary amine **36** through enamine activation [62]. Excellent enantioselectivities can be achieved for a broad range of substrates (Scheme 38.40). Water is helpful in the hydrolysis of intermediate **P** to release



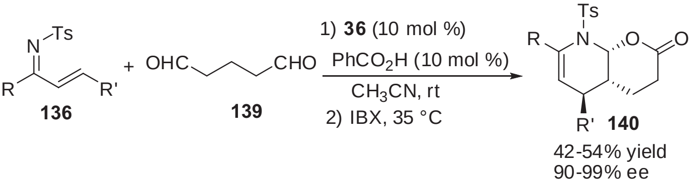


138a: R = Ph, R' = Ph, R'' = Et, 88% (97% ee)
138b: R = Ph, R' = 2-Furyl, R'' = Et, 83% (98% ee)
138c: R = Ph, R' = Me, R'' = Et, 83% (93% ee)
138d: R = Ph, R' = CO$_2$Et, R'' = Et, 95% (99% ee)
138e: R = 1-Np, R' = Ph, R'' = Et, 83% (94% ee)
138f: R = Ph, R' = Ph, R'' = BnO(CH$_2$)$_2$, 72% (99% ee)

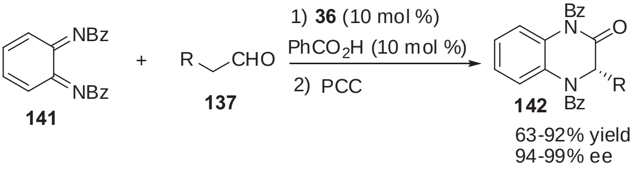
Scheme 38.40 Enamine catalysis of aza-hetero-Diels–Alder reactions.

the catalyst **36**, and the acid additive has a significant positive effect on this reaction.

When using aliphatic aldehydes tethered to arene motifs as substrates, an enantioselective sequential aza-hetero-Diels–Alder and Friedel–Crafts reaction was successfully achieved by the same group [63]. Similarly, optically active lactone[3,3-*b*] piperidine skeletons **140** can be obtained by tandem aza-hetero-Diels–Alder reaction–hemiacetal formation–oxidation from α,β-unsaturated imines **136** and glutaraldehyde (**139**) (Scheme 38.41) [64]. Enamine catalysis of the inverse-electron-demand aza-hetero-Diels–Alder reaction was further extended to *o*-benzoquinone diimide **141** by Chen's group [65]. Various hydroquinoxalinones **142** can be obtained in high yields with excellent enantioselectivities (Scheme 38.42).

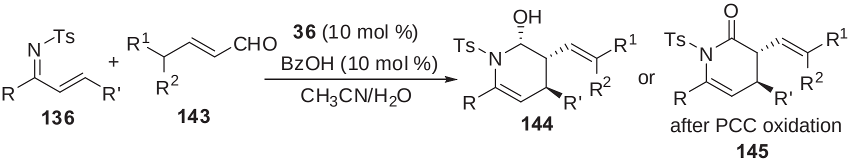


Scheme 38.41 Aza-hetero-Diels–Alder reactions with glutaraldehyde.



Scheme 38.42 Aza-hetero-Diels–Alder reactions with *o*-benzoquinone diimide.

By employing the dienamine-catalysis strategy, Chen and coworkers accomplished an unprecedented and highly regio- and stereoselective inverse-electron-demand aza-hetero-Diels–Alder reaction of α,β-unsaturated imines **136** with α,β-unsaturated aldehydes **143** [66]. Various multifunctional piperidine derivatives **144** and **145** can be obtained, with excellent levels of enantioselectivity, that are potentially useful in the synthesis of natural products and medicinal chemistry (Scheme 38.43).

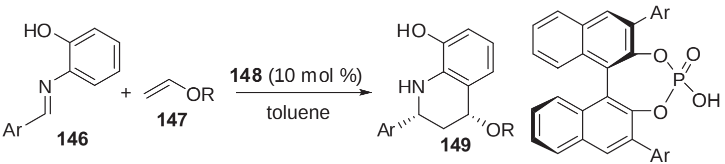


144a: R = Ph, R' = CO_2Et, R^1= Et, R^2 = H, 68% (99% ee), *E*/*Z* = 8.1/1
144b: R = 4-ClC_6H_4, R' = CO_2Et, R^1= Et, R^2 = H, 71% (98% ee), *E*/*Z* = 7.5/1
145a: R = Ph, R' = CO_2Et, R^1= Me, R^2 = Me, 95% (99% ee)
145b: R = 2-Thienyl, R' = CO_2Et, R^1= Me, R^2 = Me, 91% (99% ee)
145c: R = CO_2Et, R' = Ph, R^1= Me, R^2 = Me, 95% (>99% ee)

Scheme 38.43 Aza-hetero-Diels–Alder reactions with α,β-unsaturated aldehydes.

38.4.3
Chiral Brønsted Acids as Catalysts

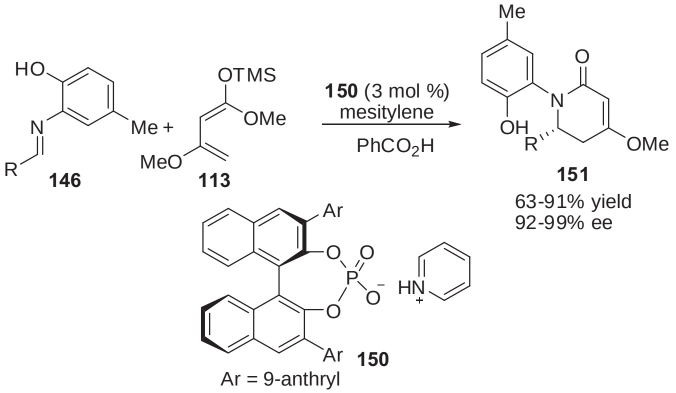
A phosphoric acid **148** bearing 9-anthryl groups on the 3,3′-positions, developed by the Akiyama group, turned out to be a highly effective catalyst for the inverse-electron-demand aza-hetero-Diels–Alder reaction of aldimines **146** with alkyl or cyclic vinyl ethers **147** [67]. Various tetrahydroquinone derivatives **149** were obtained with high to excellent enantioselectivity (Scheme 38.44). The presence of an OH moiety on the *N*-aryl group is essential for attaining high enantioselectivity. A hydrogen bond is therefore surmised to form between the hydrogen of the imine OH moiety and the phosphoryl oxygen.



149a: Ar = Ph, R = Et, 89% (94% ee)
149b: Ar = Ph, R = Bn, 76% (91% ee)
149c: Ar = Ph, **147** = dihydropyran, 95% (97% ee)
149a: Ar = 2-Np, R = ^{n}Bu, 80% (88% ee)

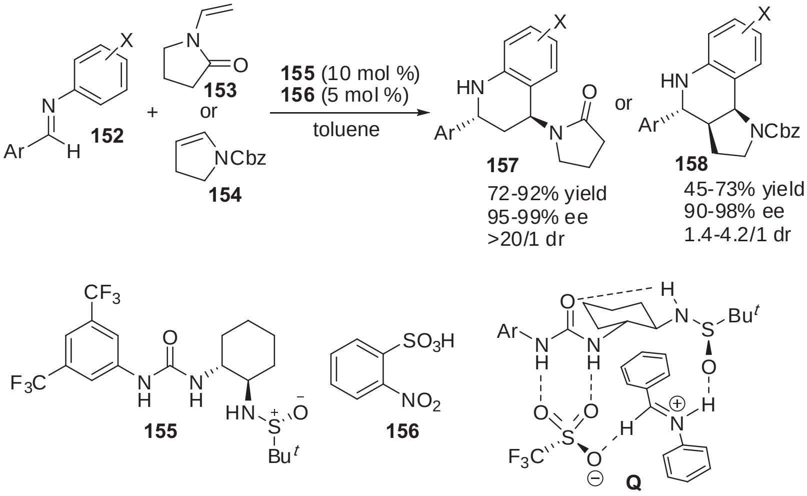
Scheme 38.44 Chiral Brønsted-acid catalyzed aza-hetero-Diels–Alder reactions.

One of the potential problems associated with **148** lies in its strong acidity, in particular when applied to labile substrates. Akiyama and coworkers have found that its pyridinium salt **150** also exhibits efficient catalytic activity as a chiral Brønsted acid catalyst that is compatible with labile substrates such as Brassard's diene **113** [68]. Accordingly, an efficient inverse-electron-demand aza-hetero-Diels–Alder reaction of aldimines **146** with Brassard's diene **113** catalyzed by **150** was accomplished to afford piperidinone derivatives **151** in high yields with excellent enantioselectivities (Scheme 38.45).



Scheme 38.45 Chiral Brønsted-acid catalyzed reactions with Brassard's diene.

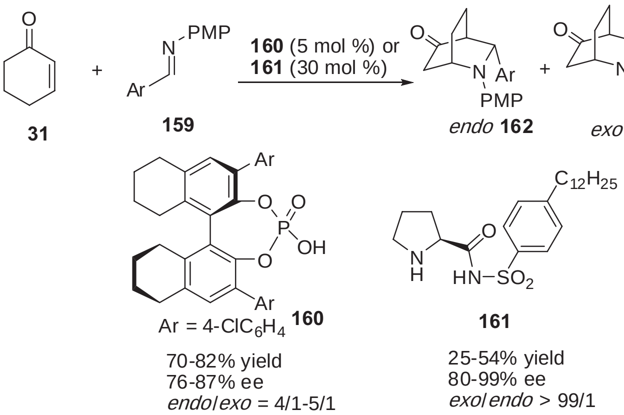
Recently, Jacobsen described a novel strategy for inducing enantioselectivity in reactions of protio-iminium ions, wherein a chiral catalyst interacts with the highly active intermediate through a network of non-covalent interactions (as shown in transition state **Q**) [69]. Accordingly, a highly efficient and enantioselective aza-hetero-Diels–Alder reaction between *N*-aryl imines **152** and enamide **153** or ene-carbamate **154** has been achieved with the use of the combination of the bifunctional sulfinamido urea derivative **155** and *ortho*-nitrobenzensulfonic acid (**156**) (Scheme 38.46). The 2 : 1 ratio of **155** and **156** was essential to ensure the complete suppression of the racemic pathway catalyzed by **156** [69].



Scheme 38.46 Cooperative catalysis of aza-hetero-Diels–Alder reactions.

In 2006, Gong and coworkers reported the first chiral Brønsted acid-catalyzed asymmetric direct aza-hetero-Diels–Alder reaction [70]. Phosphoric acid catalyst **160** exhibited excellent catalytic activity and selectivity for the reaction of cyclohexenone (**31**) with a broad range of aldimines **159** to produce N-containing heterocycles **162** with up to 87% ee (Scheme 38.47). More recently, Carter and coworker developed the modified proline catalyst **161** for this reaction, and high levels of enantioselectivity and diastereoselectivity were obtained (Scheme 38.47) [71]. Interestingly, the aromatic imines favor *exo* products while the aliphatic imines favor *endo* products.

With the use of chiral phosphoric acid catalyst **160**, Zhu and coworkers have successfully developed the first three-component inverse-electron aza-hetero-Diels–Alder reaction (Povarov reaction) [72]. A broad range of aromatic and aliphatic aldehydes **110** as well as anilines **163** were well tolerated to give

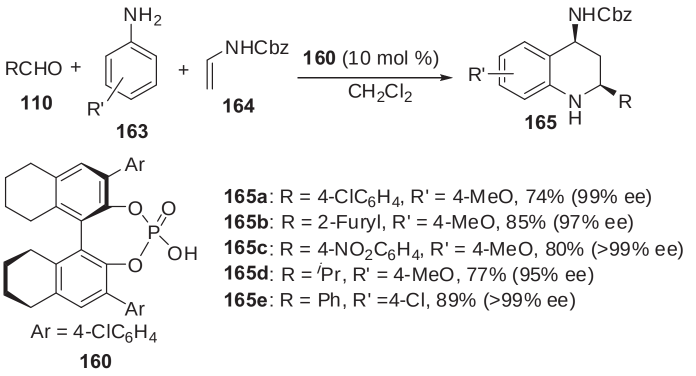


70-82% yield
76-87% ee
endo/*exo* = 4/1-5/1

25-54% yield
80-99% ee
exo/*endo* > 99/1

Scheme 38.47 Asymmetric direct aza-hetero-Diels–Alder reactions.

tetrahydroquinolines **165** with remarkable enantioselectivities (Scheme 38.48). Chiral phosphoric acid **160** is supposed to act as a bifunctional catalyst to activate the *in situ* generated imines and enecarbamate **164** simultaneously via hydrogen bonding.



165a: R = 4-ClC$_6$H$_4$, R' = 4-MeO, 74% (99% ee)
165b: R = 2-Furyl, R' = 4-MeO, 85% (97% ee)
165c: R = 4-NO$_2$C$_6$H$_4$, R' = 4-MeO, 80% (>99% ee)
165d: R = ^{i}Pr, R' = 4-MeO, 77% (95% ee)
165e: R = Ph, R' =4-Cl, 89% (>99% ee)

Scheme 38.48 Chiral Brønsted acid catalyzed three-component Povarov reaction.

38.5
Conclusion

Over the past decade, rapid growth has been achieved in organocatalytic asymmetric Diels–Alder and hetero-Diels–Alder reactions. Numerous organocatalysts such as chiral amines, guanidines, N-heterocyclic carbenes, Brønsted acids, and bifunctional catalysts have been successfully developed. The activation modes for these catalysts, such as imine-catalysis, enamine-catalysis, dienamine catalysis, trienamine catalysis, hydrogen-bonding catalysis, and so on, have also been well documented. Because of the easy access to these small organic molecules, the mild conditions, and the excellent selectivity obtained, organocatalytic Diels–Alder reactions will have a wide application in synthetic chemistry. However, relatively high catalyst loading is still one of the drawbacks or bottlenecks in the organocatalysis of Diels–Alder reactions. Further efforts to improve the organocatalyst activity and discover novel activation modes are still necessary.

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Part V
Increasing Complexity

39
Organocatalytic Radical and Electron Transfer Reactions

Thibault Gallavardin and Peter I. Dalko

39.1
Introduction

Open-shell reactions in which the critical bond forming reactions imply at least one odd valence electron shell reagent have recently moved to the center of attention [1]. This renaissance of interest in radical/radical ionic chemistry was triggered by the emergence of new paradigms, including organocatalysis, opening up new perspectives in synthesis. Several synthetically relevant highly chemo- and stereoselective transformations were described recently under remarkably mild conditions, some of them under enantiocatalytic conditions [2]. While open shell bond-forming reactions were postulated in many transformations, the true nature of the elementary steps (polar/radical ionic/radical) and, in particular, the timing of the key radical/polar crossover step of the major reaction path often remains putative and depends sensitively on reaction conditions [3].

The selective removal, or addition, of one electron from, or to, a neutral molecule makes it possible to reverse the polarity of a substrate (umpolung) and may allow reactions of otherwise nonreactive substrates. Chemically, electrochemically [4], or photochemically [5] induced ET (electron-transfer) reactions showed interesting selectivity. Conditions were found that enabled remarkably high stereocontrol, which is rather unusual in open-shell reactions considering the fast kinetics of the bond-forming step. An example of this altered reactivity can be seen in the breaking of aromaticity by one-electron oxidation of arenes, which changes the reactivity of the substrate from nucleophilic to electrophilic and thus makes it susceptible to addition of selected nucleophiles. Moreover, electrophilic radicals can be produced under SET (single electron-transfer) conditions that may allow selective combination with aromatics, as was seen in trifluoromethylation (see below) [4d, 6]. Notably, ET reactions open up perspectives with new type of experimental conditions, such as was seen with readily prepared and easily implemented flow reactors, which enable the marked acceleration of various transformations [7].

Contrary to popular tin-hydride-mediated reactions, which are realized in the presence of a catalytically generated initiator and are conducted under atom/group

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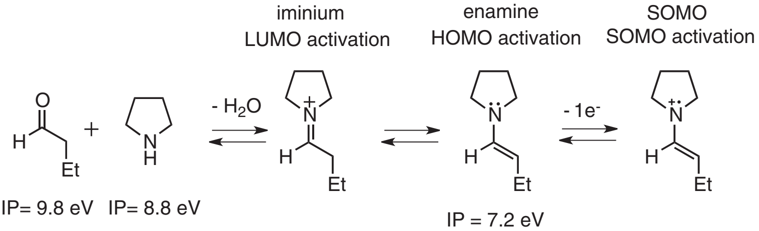
transfer chain conditions, SET reactions require either the presence of a stoichiometric amount of oxidizing, or reducing, agents, or a photochemically (re)generated ET agent. The nature of ET reactions – oxidation or reduction – is determined by the relative oxidation/reduction potential [i.e., ionization potential (IP)] of the reagents versus the substrate. The reduction potential is used to describe the potential associated with the electrochemical half-reaction written in the direction where the more oxidized species is reduced. Like acid–base reactions, electron-transfer reactions are a matched set where the direction of the ET can be determined to a good approximation by looking at the standard potential for each half-reaction of the participating reagents. ET reactions can occur with either an inner sphere or an outer sphere mechanism. Inner sphere ET occurs within a chemical bond distance and, thus, is characterized by the "physical contact" of the reagents. Inner sphere reactions are inhibited by large ligands, as can be seen in biological systems, where redox sites are often shielded by bulky proteins. Most of the *synthetically productive* ET reactions imply at least one inner sphere step, however. The bridging ligand is classically a halide, or can be, for example, a thiocyanate. Formation of the ET complexes is highly reversible although this path remains enthalpically more favorable than outer sphere electron transfer (ET across a larger distance). Among synthetically useful asymmetric open shell organocatalytic reactions are SET oxidation of catalytically formed enamines, or enolates, forming 3π-radical cation species; in turn, electron-deficient alkyl radicals can be generated via, for example, reduction of an alkyl halide by using a suitable ET catalyst.

39.2
Chemically Induced Oxidative Electron-Transfer Reactions

The term SOMO activation (for self-occupied molecular orbital activation) in organocatalytic reactions was coined by the MacMillan group and signifies the one-electron oxidation of an enamine intermediate giving rise to a $3e^-$ radical–cationic SOMO intermediate. The electron-poor radical cationic intermediate reacts preferentially with an electron-rich SOMOphile reagent (a path called "SOMO activation"). In turn, the electron-rich enamine intermediate can be a SOMOphile reagent and may combine with an electron-poor radical intermediate present in the reaction ("SOMOphile" pathway) [1e]. SOMO organocatalytic reactions can be considered as variations of enamine and imine organocatalysis, which give access to an alternative reactivity compared to common nucleophile/electrophile activation. Such redox catalytic cycles can be engineered as, for example, two parallel interwoven catalytic cycles generating simultaneously an electron-rich enamine from the condensation of an aldehyde and an amine catalyst, and an electrocatalytic/electron transfer cycle with a suitable oxidizing, or reducing, agent.

For the efficient design of SOMO organocatalytic reactions three key design elements should be considered:

1) First, a selective ET reaction, meaning either the oxidation or reduction of the substrate, is imperative. The fact that enamine is (usually) more reactive in oxidation reactions than the other substrates in the mixture (such as the starting aldehyde, for example) can be understood by considering the relative ionization potentials of these compounds; they are also key parameters in determining the viability of the ET approach. The fact that the ionization potentials of enamines are lower than those of the aldehyde starting materials (by roughly 1.6 eV in the case of butanal; Scheme 39.1) indicates that enamine is more prone to one-electron oxidation than the starting aldehyde; it is also lower, than other species in the reaction mixture such as the amine catalyst ensuring productive chemistry and selectivity. A striking aspect of organocatalytic SET oxidation reactions is that electron-rich heteroaromatic systems that are often susceptible to mild oxidants can be rendered compatible. Synthetically productive chemically induced ET reactions were generated under asymmetric organocatalytic conditions by using either a stoichiometric amount of transition-metal oxidant such as Ce^{4+} (CAN, ceric ammonium nitrate) and Fe^{3+} or more complex, catalytic amounts of metal complexes with a bulk inorganic oxidant ($Cu^{2+}/Na_2S_2O_8$) (*vide infra*).



Scheme 39.1 Formation of SOMO activated chiral intermediate upon preferential oxidation of enamine.

2) The second design element is identification of a chiral amine catalyst that could provide high levels of enantiodiscrimination in the subsequent bond-forming processes. To date, almost all enantioselective ET organocatalytic transformations have been realized by using MacMillan's imidazolidinone catalysts, such as **1**, which showed superior selectivity to any other catalyst system (Figure 39.1). While **1** was the catalyst of choice in many reactions, the structure was also optimized for increased stability against oxidative decomposition as well as for better selectivity and reactivity. Notably, the sense of asymmetric induction observed was consistent with the enamine/iminium reactions of similar systems. By analogy to these well-established organocatalytic transformations, and also in accordance with DFT analysis, the imidazolidinone catalyst selectively forms an enamine that projects the 2p electron away from the bulky *tert*-butyl group, whereas the electron-rich olefin selectively populates an (*E*)-configuration to minimize nonbonding interactions

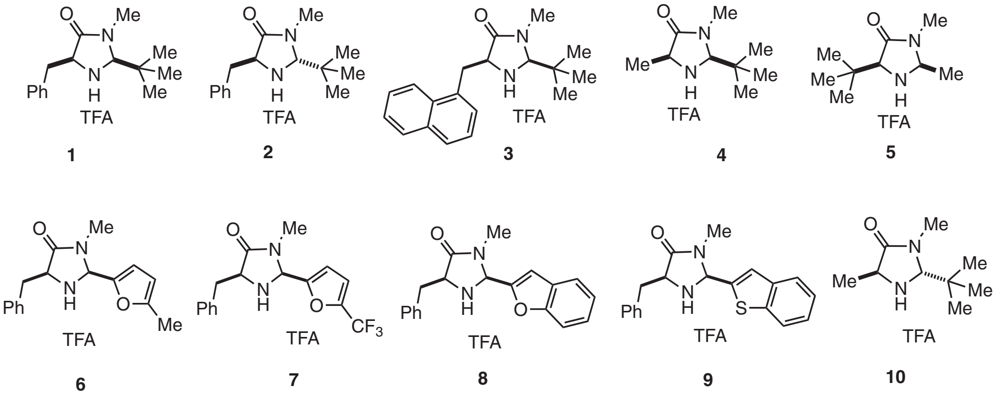


Figure 39.1 Representative chiral imidazolidinone catalysts used in SOMO activation.

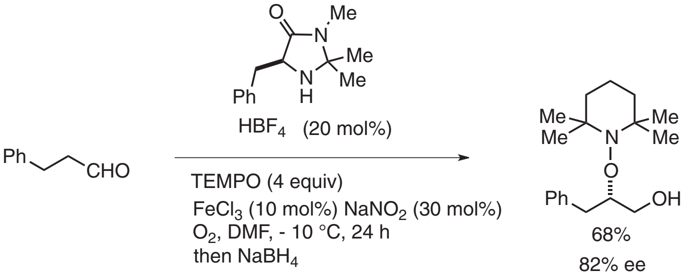
with the imidazolidinone ring (Scheme 39.1; see also in Chapter 5 for further details). A molecular orbital (MO) analysis showed that the largest coefficient of the singly occupied π orbital lies on C(2) and the charge is mainly associated with the nitrogen, as in ammonium cations [6d]. The species is of course a resonance hybrid, but is best characterized as an alkyl radical conjugated to an iminium cation. According to the original model, the activated radical would position the 3π-electron system away from the bulky *tert*-butyl moiety, while the asymmetric element (usually a benzyl group, in the most current catalysts Figure 39.1) would effectively shield the *Re*-face, such that nucleophile addition may occur preferentially from the less shielded *Si*-face.

3) Finally, the last critical element is the propensity of the SOMO intermediate to engage in stereodefined C–C bond formation with a large variety of π-rich nucleophiles. In fact, electron-deficient radicals are known to rapidly combine with electron-rich olefins to forge even the most elusive C–C bonds; electron rich radicals would combine, in turn, with electron-poor olefins. Stabilization of the transient radical/radical ion is a key thermodynamic factor and is the origin of the observed chemoselectivity of the given transformation. ET radical reactions are characterized by low-barrier activation as the addition steps in open-shell reactions are energetically less demanding than in polar transformations. As the overall charge of the reacting centers is low, and thus they are weakly solvated, the kinetics of the radical cation reaction is dramatically superior compared to polar reactions. A close to first-order rate was observed in the allylation of enamines, with the rate-determining step being the electron-transfer step to the enamine [3b]. In this context the high stereoselectivity of several transformations is remarkable, a mechanistic feature not traditionally associated with radical activation. ET reactions are characterized thus by mild reaction conditions (reaction temperature below ambient) and usually shorter reaction times than for ionic transformations.

Chemically induced ET reactions rely on complex sequences in which the solvent, and in particular water, plays a key role [3b]. Solvent molecules may (and usually do) modify the structure of the ET reagent, and thus the oxidizing/reducing potentials. The many influences of water can be illustrated by the modulation of the efficiency of the oxidation of an enamine by CAN. Indeed, a small amount of water (ca. 0.3 equiv.) is necessary to ensure catalytic turnovers, while an excess of water shifts the equilibrium towards aldehyde and free catalyst. In the heterogeneous system water also determines the stationary concentration of CAN, which remains mainly insoluble in the reaction mixture. Finally, water can also participate in the reaction as cation scavenger, as was seen, for example, in the capture of the putative silyl-cation intermediate in the allylation reaction (see below).

39.2.1
Oxamination Reactions

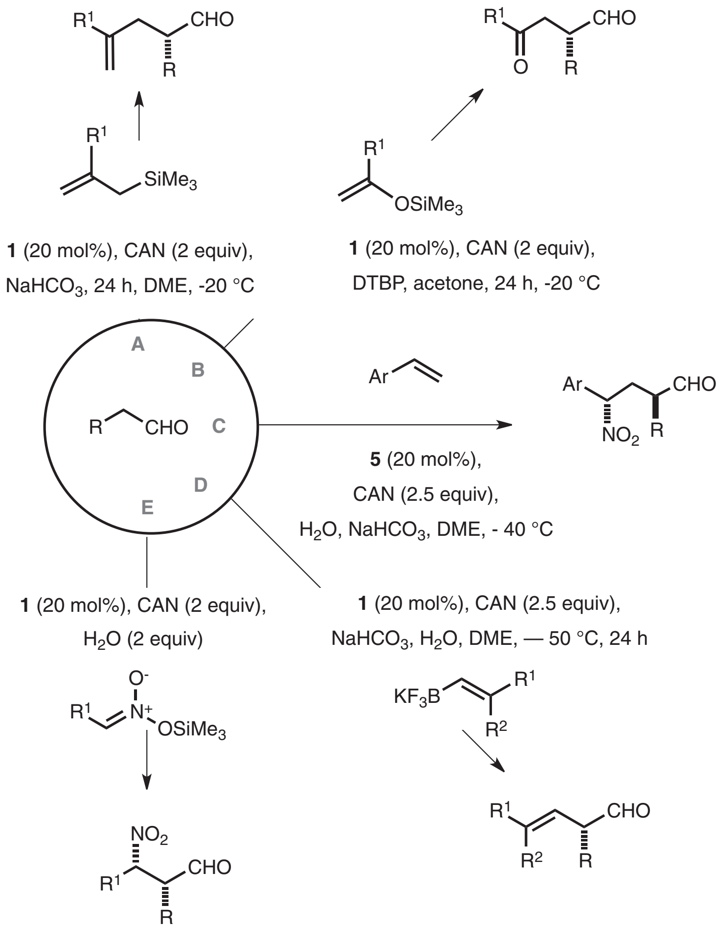
Electron-transfer/organocatalytic reactions were postulated in oxamination reactions [9]; later it was demonstrated [10] that the reaction follows preferentially a polar enamine activation manifold: when $FeCl_3$ was used in DMF as oxidizing agent the metal coordinates rapidly to the nitroxyl radical of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) (Scheme 39.2) [11]. SOMO conditions were find by replacing the metal salt by a non-coordinating oxidizer such as tris(*p*-bromophenyl) aminium hexachloroantimonate [12]. Under these conditions the ET reaction arguably afforded the enamine radical cation, which was trapped by TEMPO, or by styrene as a purported SOMOphile partner.



Scheme 39.2 Asymmetric oxamination of dihydrocinnamaldehyde.

39.2.2
Additions to Olefins and Alkynes

The MacMillan group developed an impressive array and complexity of highly enantioselective SOMO transformations with the addition of enamine-derived radical cations to electron-rich olefins, allowing the allylation, enolation, vinylation, styrenation, chlorination, polyene cyclization, arylation, benzylation, and alkylation of a range of aldehydes (Scheme 39.3) [1e, 5a, 5b, 6, 8c, 13]. A common mechanistic

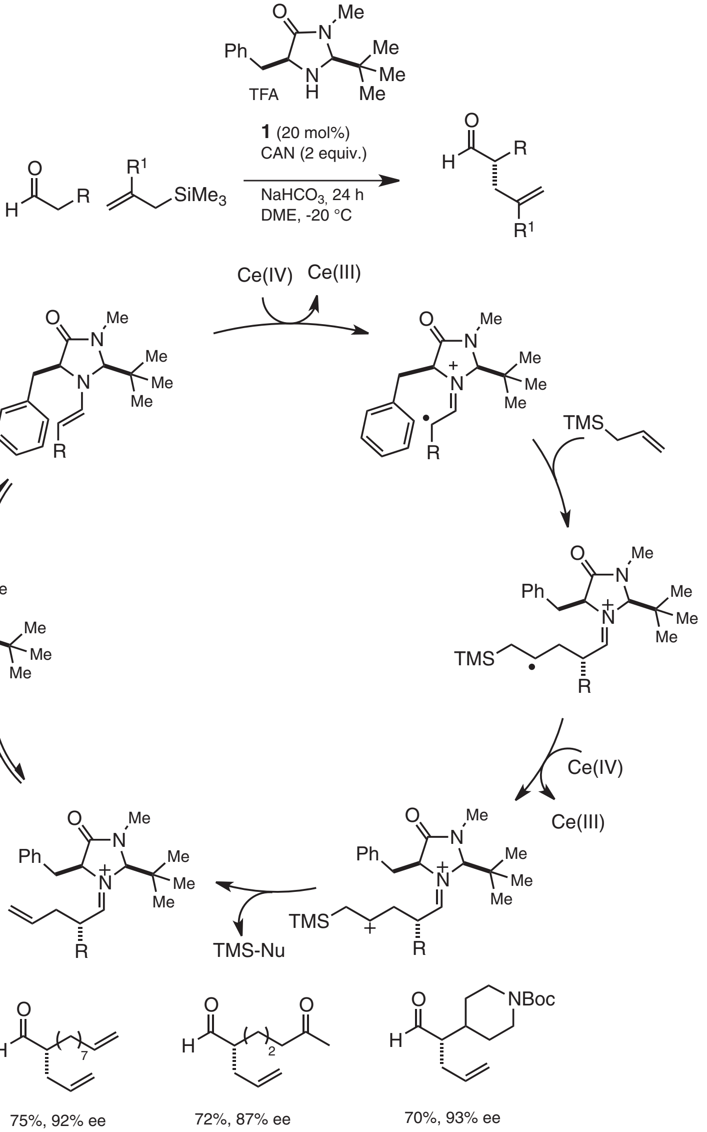

1 (20 mol%), CAN (2 equiv),
NaHCO3, 24 h, DME, -20 °C
1 (20 mol%), CAN (2 equiv),
DTBP, acetone, 24 h, -20 °C
A
B
C
D
E
5 (20 mol%),
CAN (2.5 equiv),
H2O, NaHCO3, DME, - 40 °C
1 (20 mol%), CAN (2 equiv),
H2O (2 equiv)
1 (20 mol%), CAN (2.5 equiv),
NaHCO3, H2O, DME, — 50 °C, 24 h

Scheme 39.3 Oxidative (CAN-mediated) asymmetric SOMO alkylation of aldehydes.

feature of these transformations is the formation of the stabilized α-silyl, α-borato, or α-benzylic cation intermediates after a radical–polar crossover (i.e., the second ET) step [14]. The formed cation intermediate can regioselectively collapse to render an olefinic or carbonyl containing product, or may capture diastereoselectively an anionic or neutral heteroatom addend (e.g., NO^{3-}, Cl^-, H_2O), affording a homoaldol-type alkylation product (Scheme 39.3, paths A–D). α-Nitroalkylation (path E) transforms aliphatic aldehydes and a series of silyl nitronates into chiral β-nitro aldehydes, which are potential precursors of β-amino acids.

39.2.3
Asymmetric Intermolecular Allylation of Aldehydes

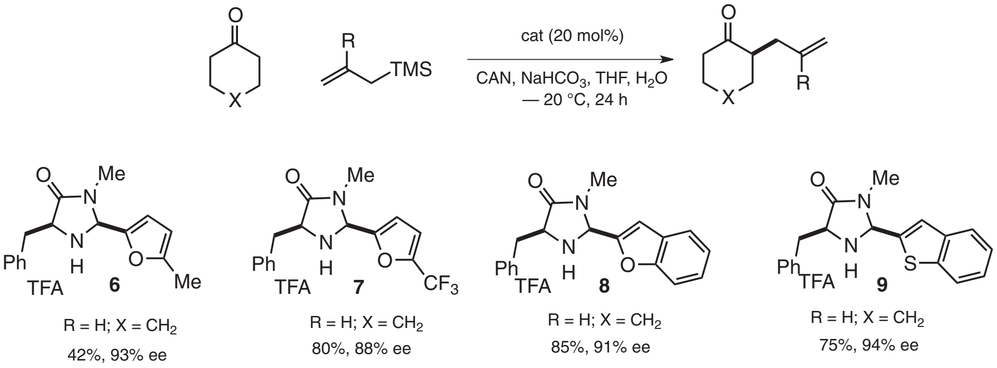
An asymmetric organocatalytic ET reaction was developed for the allylation of aldehydes with allylsilanes as electron-rich SOMOphile compounds [1e]. Key elements of the reaction are the addition of the radical cation intermediate to the allylsilane reagent, oxidation of the β-radical to carbocation by a second ET, and E_1 fragmentation of the β-silyl carbocation to form the terminal olefin. When catalyst **1** was used in 1,2-dimethoxyethane (DME) in the presence of 0.3 equiv. of water, at low temperature (–20 °C), products were formed in high enantioselectivity (Scheme 39.4).



Scheme 39.4 Organocatalytic SOMO allylation and the catalytic cycle.

39.2.4
Asymmetric Allylation of Ketones [15]

The difficult translation of SOMO activation to cyclic ketones was achieved with the help of catalyst **6**, which was developed earlier for Diels–Alder reactions of cyclic ketones via iminium activation. The difficulty lies in the fact that aldehydes and ketones exhibit largely different steric and electronic properties with respect to catalyst interactions [16]. Competitive catalyst degradation under the oxidative conditions (i.e., oxidation of the methyl group attached to furan) was circumvented by transforming the methyl into a trifluoromethyl group, or by direct replacement of the furyl ring with less electron-rich heteroaryl systems such as benzofuran (**8**) or benzothiophene (**9**), which are less sensitive to oxidation (Scheme 39.5).



Scheme 39.5 SOMO allylation of cyclohexanone using imidazolidinone catalysts **6–9.**

As the allylated enamine has higher reactivity (i.e., lower ionization potential) the selective mono-allylation of cyclohexanone required excess (2 equiv.) ketone reagent. Nevertheless 20 equivalents of cyclobutane were necessary for the selective reaction with cyclobutanone and only 2,5-bis-allylated cyclopentanone was obtained, as the second oxidation occurred immediately on the iminium intermediate prior to hydrolysis with this substrate. The allylation reaction was compatible with alkyl and heteroatom substituents at the β and γ positions. When non-symmetrical heteroatom containing substrates were used, C(4) allylation occurred selectively in high yields (70–86%) and in high ee (80–99%) (Figure 39.2).

39.2.5
Intramolecular Asymmetric Allylations

SOMO allylation can be realized under intramolecular conditions, giving access to enantiomerically enriched five–seven-membered rings [17]. Similar to intermolecular reactions, catalyst **1** showed superior selectivity and efficiency in acetone

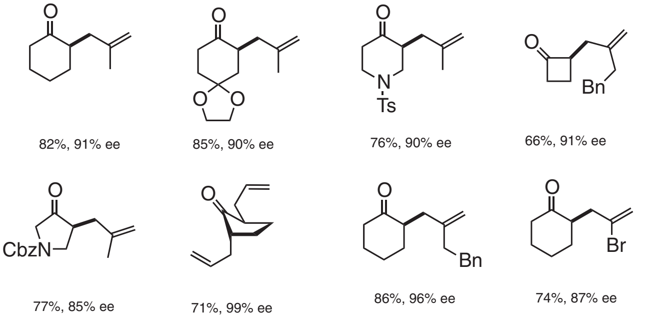
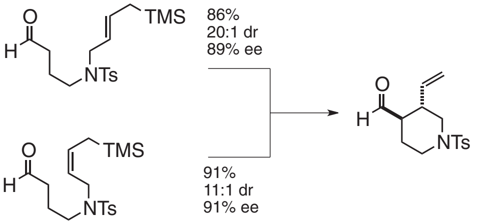


Figure 39.2 Products of asymmetric intermolecular allylation of symmetric cyclic ketones using catalyst **8.**

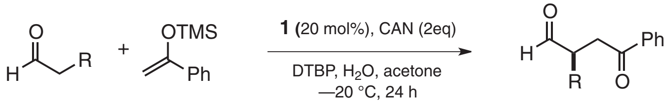
at −20 °C. Intriguingly, (*E*)-allylsilanes cyclized with slightly higher levels of diastereocontrol than the corresponding (*Z*)-substrates, while the reverse trend was observed in the enantioselectivity (Scheme 39.6).



Scheme 39.6 Influence of olefin geometry on the selectivity of intramolecular asymmetric allylation under SOMO conditions.

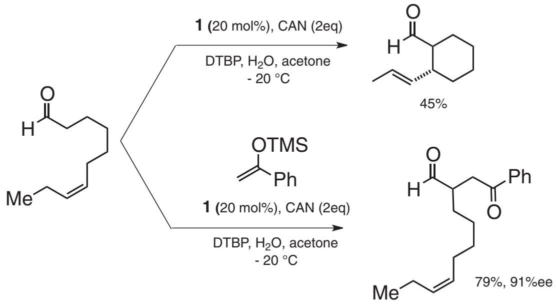
39.2.6
α-Enolation [8a]

In the α-enolation of aldehydes electron-rich enolsilanes are used instead of allylsilanes as SOMOphile reagents. Best results were obtained in the presence of catalyst 1, CAN (2 equiv.), and 2 equiv. of H_2O as well as 2 equiv. of 2,6-di-*tert*-butylpyridine (DTBP) (Scheme 39.7). The mild conditions are compatible with a significant latitude in the steric demand of the SOMOphilic substituent. The presence of alkenes, sensitive aromatics, as well as alkyl, vinyl, and aryl substituted silyl enol ethers were accommodated without loss in reaction efficiency or enantiocontrol (55–85% yield, 86–96% ee). Notably, the reaction is compatible with vinylogous substrates by using the appropriate starting enolsilane. The incorporation of bulky silyl groups to prevent substrate hydrolysis in the case of alkyl substituted enolsilanes provided slightly higher enantioselectivity.



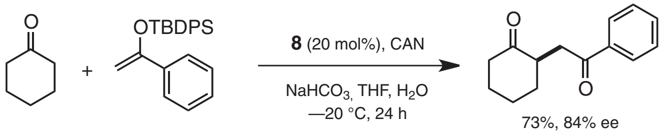
Scheme 39.7 α-Enolation of aldehydes in the presence of catalyst **1** and CAN.

Enolsilanes are more reactive than alkenes in SOMO alkylation, as was demonstrated in a competing intra- versus intermolecular experiment. As depicted in Scheme 39.8, enolsilane derived from acetophenone provided intermolecular alkylation rather than the cycle as major product.



Scheme 39.8 Competing intra- versus intermolecular reaction in which enolsilane derived from acetophenone provided the intermolecular alkylation product as major product.

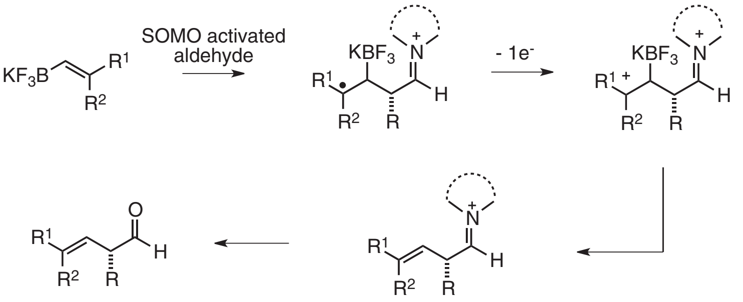
Notably, reaction conditions developed for the allylation of ketones could also be used for the direct α-enolations of symmetric ketones (Scheme 39.9).



Scheme 39.9 Enantioselective α-enolation of cyclohexanone.

39.2.7
α-Vinylation

Asymmetric SOMO vinylation of aldehydes was achieved with the vinyl potassium trifluoroborate salt of terminal alkenes, such as benzylvinylene, under SOMO-conditions, using catalyst **1** and CAN as one-electron oxidizing agent (Scheme 39.10) [16]. In this reaction the radical intermediate of the addition product was oxidized by a second equivalent of CAN, providing the cationic intermediate, from

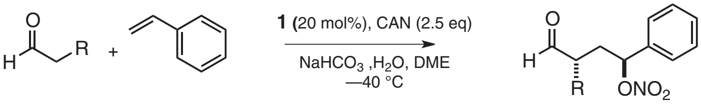


Scheme 39.10 α-Vinylation of alkenes providing *trans*-selective β,γ-deconjugated enones.

which the alkene end-product was obtained after the elimination of potassium tetrafluoroborate (i.e., the *trans*-selective Peterson-type fragmentation), affording the β,γ-unsaturated (*E*)-isomer.

39.2.8
Carbo-Oxidation of Styrenes

The transient γ-cation of the α-vinylation reaction, formed after a radical–polar crossover (i.e., a second SET oxidation) step, can be captured by a nucleophile present in the mixture, such as the nitrate counter-anion of the CAN reagent. When catalyst **1** was used, the reaction generated products in moderate dr but in high ee (Scheme 39.11).

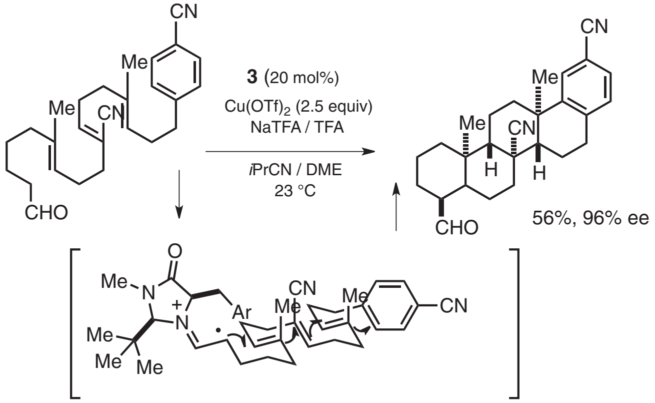


R = *n*-hex
dr = 3 : 1

Scheme 39.11 Carbo-oxidation of styrene when the transient γ-cation is intercepted by the nitro group of CAN.

39.2.9
Polyene Cyclizations [13b]

The primary radical cation intermediate [14] can be also intercepted and used directly in cascade radical cyclizations [13b]. In the sequence illustrated in Scheme 39.12 the generated putative radical cation engages in a series of 6-*endo trig* radical cyclizations with the tethered polyene terminated by a suitable arene. The selectivity of the polycyclization is guided by alternating polarity-inverted C=C bonds (acrylonitrile and isobutene moieties) favoring the 6-*endo-trig* mechanism over the

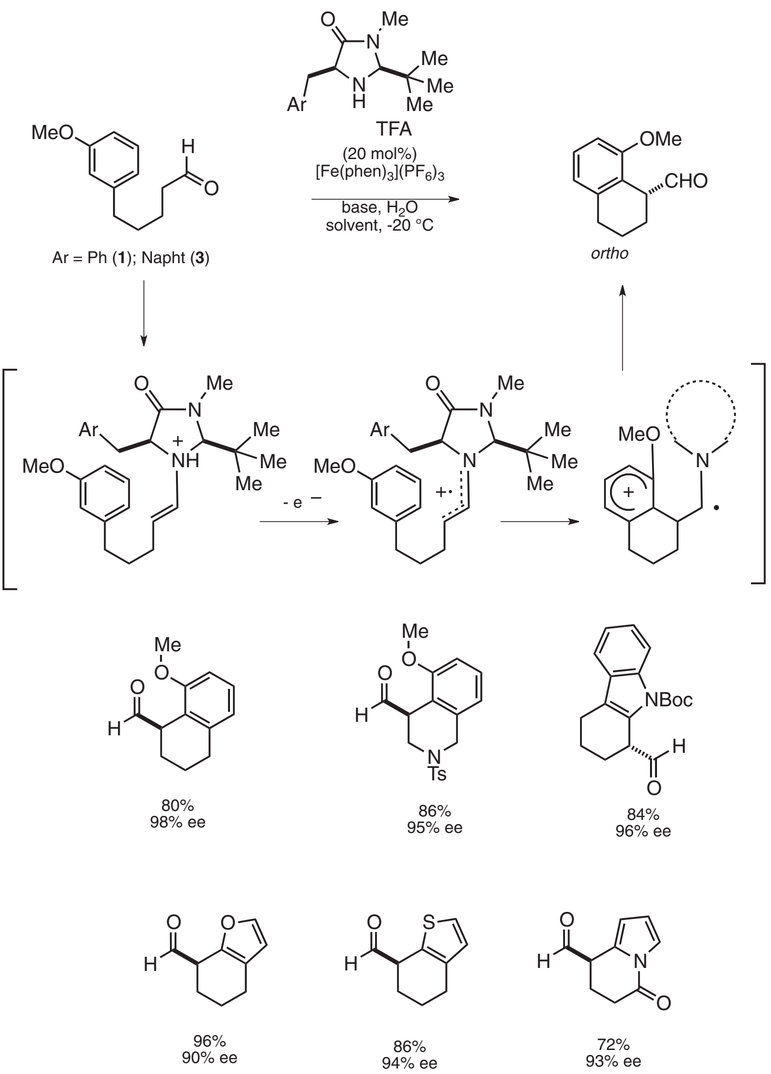


Scheme 39.12 Asymmetric template-mediated polyene cyclization under chemically induced one-electron oxidation conditions.

5-*exo-trig* process. Notably, strong oxidants that had been successful in previous SOMO activation studies {e.g., CAN and [Fe(phen)$_3$](PF$_6$)} were inefficient in this transformation. In contrast, the slow addition of Cu(OTf)$_2$ oxidant in acetonitrile with sodium trifluoroacetate (NaTFA) as a base with the naphthyl-modified catalyst **3** gave rise to synthetically useful results over a range of substrates and reaction concentrations, producing a single diastereomer in high ee. The selectivity of the reaction depends sensitively on the substituent pattern. In the presented entry the cyano group polarizes the alkene, and the disubstituted sp^2 carbon ensures efficient 6-*exo trig* cyclization versus the five-membered ring product. The end-step of the cascade cyclization is optimized by aromatic rings having electron-withdrawing groups in the *meta* position.

39.2.10
Intramolecular α-Arylation

Intramolecular α-arylation allows access to α-formyl-α-aryl substrates [8d, 18, 19]. Optimum conditions were found with imidazolidinone catalysts **1** and **3** (20 mol%) when CAN [18] or [Fe(phen)$_3$](PF$_6$)$_3$ [8d] was used as oxidant; the presence of pivalic acid and water additives boosted the efficiency of the reaction. According to the mechanistic rationale, cyclization of the enamine radical cation gives rise to the bicyclic radical cation that upon further oxidation generates a dienyl cation that collapses by rearomatization (Scheme 39.13). The transformation is *ortho*-selective when 1,3-disubstituted aryl rings are used while 1,3,4-trisubstituted aryl aldehydes give rise to *para*-substituted products [18]. This selectivity was attributed to the activation energy differences and also to the relative stabilities of the isomeric transition states [6d]. When the transition state is distorted from planarity, the energy of the *ortho,meta* transition states is augmented with respect to the *para,meta* isomers. Anisole, naphthalene, indole, pyrrole, thiophene, and furan ring systems

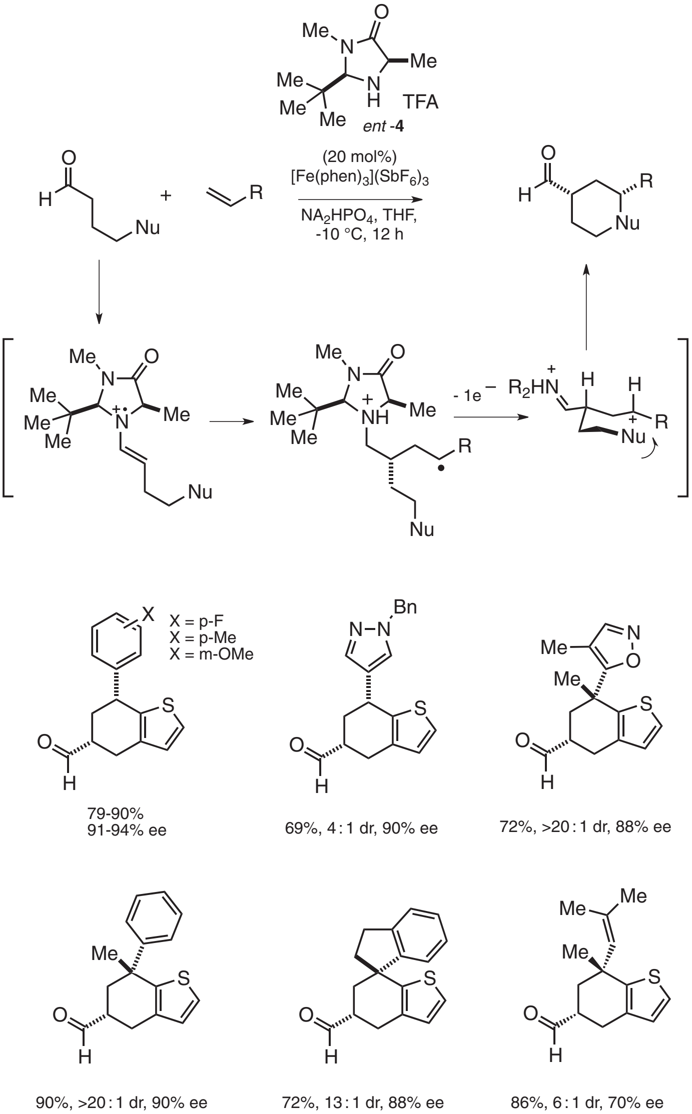


Scheme 39.13 Mechanistic rationale of the *ortho*-selective intramolecular α-arylation and reaction scope with catalyst **3** (Ar = Napht).

showed high yields and enantioselectivity. Moreover, aldehydes that incorporate nitrogen, oxygen, or carbonyl containing tethers worked well in this protocol.

39.2.11
Cascade Cycloadditions

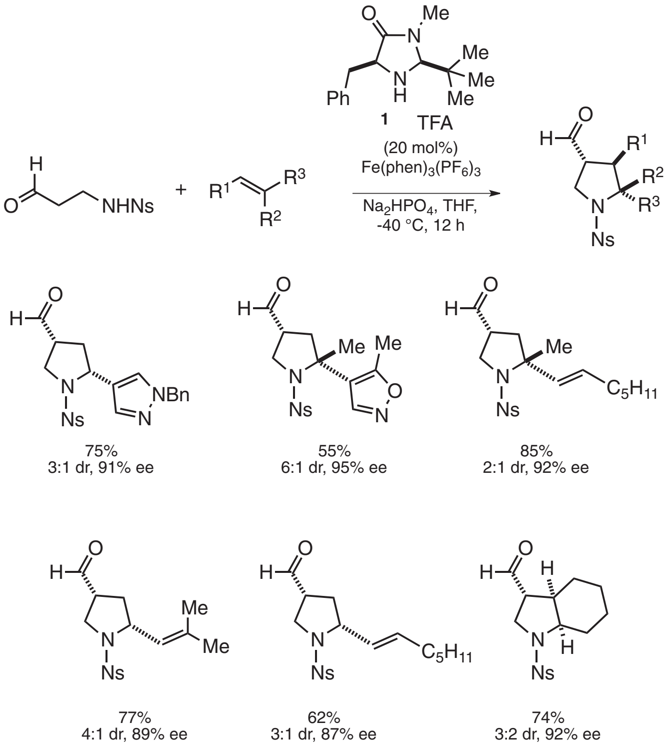
The SOMO [4+2] cascade cycloaddition employs 3-arylpropionaldehydes having electron-rich aromatic rings, such as indoles, anisoles, catechols, benzofurans, thiophenes, and olefins, or styrene reagents used in excess. The reaction affords cyclohexyl motifs with highly predictable regio-, diastereo-, and enantiocontrol [20]. The π-nucleophile-tethered aldehyde is oxidized under SOMO conditions in the presence of imidazolidinone catalyst *ent*-**4**, forming a radical cation intermediate that adds to the olefins (Scheme 39.14). Analogously to previous examples, a radical–polar crossover of the putative radical intermediate furnishes a carbocation



Scheme 39.14 Mechanistic rationale of the SOMO [4+2] cascade cycloaddition and the reaction scope.

[21] that triggers a stereoselective π-nucleophile ring closure to deliver a cyclohexyl motif. The cyclization is stereoselective based on the kinetic preference for chair-like transition states wherein pseudo-ring substituents are located in equatorial orientations. Notably, in this transformation Ce(IV) was replaced by Fe(III) bearing non-nucleophilic counterions such as PF^{6-}, AsF^{6-}, and SbF^{6-}. Furthermore, the diastereoselectivity of the cyclization varies with the function of the oxidant counterion (with the largest counterion, SbF^{6-}, being the most selective). A possible explanation of this trend can be given by examining the stereo-determining transition state, in which the chair-like conformation is more ordered (or later) when the intermediate carbocation is paired with a more polarizable or stabilizing counterion such as SbF^{6-}. α-Substituted styrenes give rise to quaternary benzylic centers with good to excellent diastereocontrol (13 : 1 dr, 88% ee). Vinyl heteroaromatics also participate efficiently in this protocol to incorporate electron-deficient ring systems.

The reaction was extended to [3+2] coupling of aldehydes and conjugated olefins with various N-protected β-amino aldehydes to olefins (Scheme 39.15). The best conditions were found with 2 equivalents of $[Fe(phen)_3](PF_6)_3$ as SET oxidant in the presence of amine catalysts **1**, although the reaction proceeded in a less



Scheme 39.15 SOMO [3+2] cascade cycloaddition and the reaction scope.

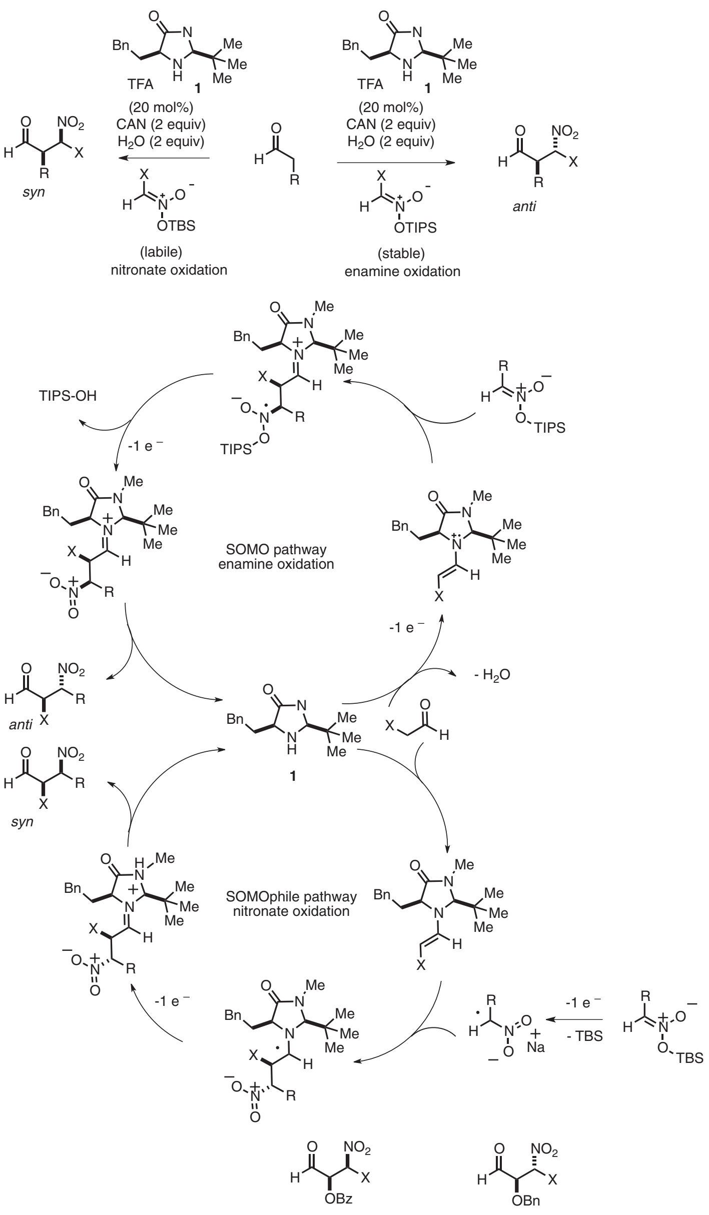
diastereoselective manner compared to the six-membered counterparts [22]. Interestingly, a correlation has been found with the electron-withdrawing capacity of the amine protecting group (Cbz < Ts < Ns), as better diastereocontrol was achieved with stronger electron-withdrawing groups, suggesting a more ordered (later) transition state with less nucleophilic amides.

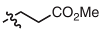
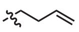
39.2.12
Asymmetric Nitroalkylation of Aldehydes

Nitroalkylation of aldehydes may provide products with either *anti* or *syn* selectivity, depending on the reaction conditions used (Scheme 39.16) [13a]. The transient radical cation may be intercepted by a silyl nitronate, or the nitronate may undergo oxidation to form a nitronate radical cation that could rapidly trap the enamine. At this stage, a second oxidation event in each pathway provides the same iminium intermediate that upon hydrolysis and subsequent Si–O bond cleavage leads to the desired β-nitroaldehyde adduct. A relationship between the diastereoselectivity of the reaction and the inherent lability of the silyl nitronate used was found. For example, relatively labile silyl groups such as TBS, TMS, and TES preferentially provided the *syn* diastereomer while TBDPS and TIPS nitronates provided *anti* diastereocontrol with a useful degree of selectivity in particular with TIPS. The variation of the *syn*/*anti* selectivity was attributed to modification of the paths that the reaction followed. If a relatively labile silyl group-protected reagent was used, such as TBS nitronate, a rapid oxidation occurred, generating a nitronate radical cation preferring, thus, a SOMOphile pathway (in which the enamine reagent plays the role of the SOMOphile) giving access to a *syn* adduct. In turn, the TIPS nitronate substrate afforded *anti*-selective coupling, with the primary pathway involving enamine oxidation.

39.3
Photoredox Catalysis

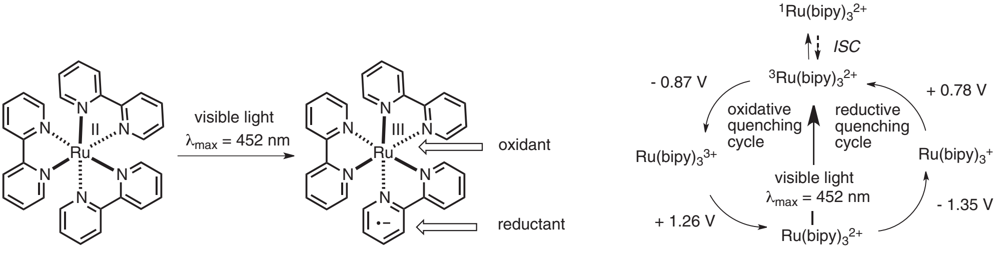
The combination of organocatalysis with photoredox reactions provides further opportunities for developing new enantioselective transformations [3a, 7, 23]. With operational simplicity, chemically productive asymmetric organocatalytic photoinduced ET conditions were found in the presence of a catalytic amount of photoredox sensitizers such as $[Ru(bipy)_3]^{2+}$ or $[Ir(ppy)_2(dtb\text{-}bipy)]^{+}$ (bipy = bipyridine, ppy = 2-phenylpyridine, dtb-bipy = 4,4-di-*tert*-butyl-2,2-dipyridyl) [5a,b], or with an organic sensitizer such as eosin Y [5c, 24]. Chemically productive triplet sensitized photoredox catalysts are produced by irradiation at the appropriate wavelength upon forming the singlet excited state that is converted rapidly by internal (intersystem crossing [ISC]) conversion into a long-lived triplet excited state. As direct de-excitation is electronically forbidden, fluorescence and internal conversion are minor deactivation pathways. Furthermore, the formed triplet state is sufficiently long-lived to undergo bimolecular redox quenching reactions. These triplet-excited



	(with TBS-nitronate)	(with TIPS-nitronate)
X = Me	74%; 4:1 dr; 94%ee	73%; 6:1; 87%ee
X = 	68%; 6:1 dr; 91%ee	79%; 6:1; 91%ee
X = 	91%; 5:1 dr; 91%ee	73%; 2:1; 80%ee

Scheme 39.16 Mechanistic rationale of the SOMO nitroalkylation of aldehydes and the reaction scope.

organometallic complexes are best described by oxidations of the metal center and reductions of the ligands, such as represented in Scheme 39.17 for Ru(bipy)$_3$Cl$_2$, as a prototypical photoredox catalyst, having thus both oxidizing and reducing capacity.



Scheme 39.17 Ru(bipy)$_3$Cl$_2$ as a prototypical photoredox catalyst and quenching cycles.

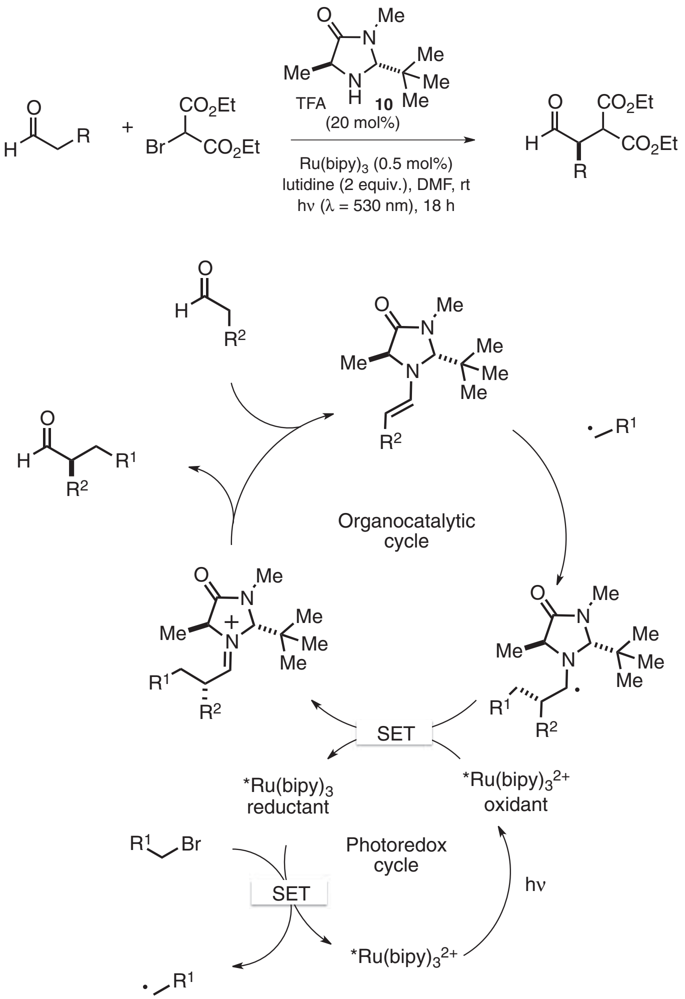
The great majority of photoredox reactions rely on reductive electron-transfer process to an alkyl halide (usually a bromide) generating an electron-deficient alkyl radical. The so-formed electrophilic radicals can be trapped by electron-rich olefins by intra- or intermolecular reaction [25].

39.3.1
α-Alkylation of Aldehydes

The enantioselective catalytic α-alkylation of aldehydes with malonyl, acetophenyl, benzyl, or fluoroalkyl halides was realized with the simultaneous use of electron-transfer reagent and organic catalysis [24]. The transformation is engineered on two interwoven catalytic cycles, that is, the photocatalytic redox cycle, which provides the SOMO-activated radical, and the enamine cycle, which generates the SOMOphile enamine.

For the alkylation of aldehydes by α-bromomalonates, the Ru(bipy)$_3^{2+}$ complex was used as redox catalyst, which can be excited at 465 ± 20 nm (500 mW) to populate the *Ru(bipy)$_3^{2+}$ metal-to-ligand charge transfer (MLCT) excited state. The photo-excited *Ru(bipy)$_3^{2+}$ is a relatively strong reductant with a reduction potential of −1.33 V versus saturated calomel electrode (SCE) in CH$_3$CN (NB the reduction potential of the complex can be tuned by modification of the ligand).

In the α-alkylation of aldehydes, initiation of the photocatalytic cycle relies on sacrificial oxidation of the electron-rich substrate – enamine (or, eventually, arene) – and a reductive electron transfer to the α-bromocarbonyl substrate rapidly furnish the electron-deficient alkyl radical while returning Ru(bipy)$_3^{2+}$ to the catalytic cycle (Scheme 39.18). The electrophilic radical then adds to the generated chiral enamine formed by a parallel aminocatalytic cycle. The thus-formed electron-rich α-amino radical is oxidized by the Ru complex to produce the iminium ion and regenerate the active reductant, Ru(bipy)$_3^{2+}$ – a step that closes the photoredox

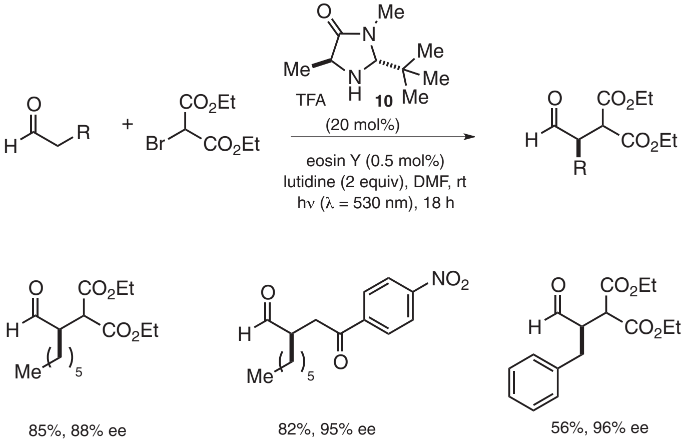


Scheme 39.18 α-Alkylation of aldehydes and mechanistic rationale.

cycle. In the ultimate step of the sequence hydrolysis of the iminium regenerates the amine catalyst while delivering the enantioenriched α-alkylated product.

The organometallic sensitizer can be replaced by a purely organic dye such as eosin Y that acts as a photoredox catalyst after excitation with visible light and gives rise the more stable triplet state [26]. In the presence of eosin Y and MacMillan's "*trans*-methyl" imidazolidinone catalyst **10** and substrates (aldehyde and α-bromocarbonyl compounds) the alkylation reaction performed similarly while requiring somewhat longer reaction times at the optimal –5 °C temperature.

The low quantum yield (6–9%) as well as the observed amplifying "dark reaction" may be a sign of a more complex reaction course, however, compared to what is depicted in Scheme 39.19.

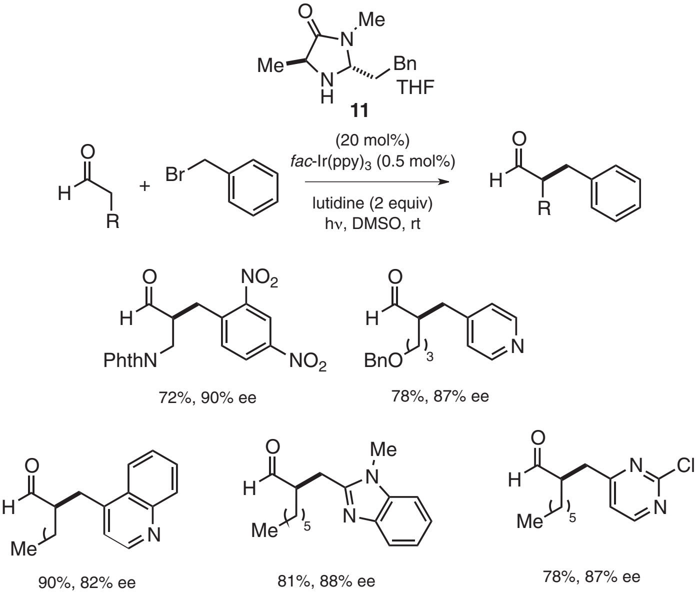


Scheme 39.19 Asymmetric α-alkylation of aldehydes with eosin Y as photosensitizer and the reaction scope.

The redox catalyst can be also replaced by the appropriate combination of heterogeneous semiconductor photocatalysts. The use of white TiO_2 or covalently surface-modified TiO_2 by Phos-Texas Red dye (Phos-Texas-Red–TiO_2) allowed similar yields and stereoselectivities in the α-alkylation reaction compared to reactions with Ru complexes [27]. According to the rationale, an electron transfer from the conduction band of the semiconductor to the halogenated carbonyl results in the loss of a bromide anion and generates the α-carbonyl radical. The so-formed radical adds to the enamine obtained by condensation of the chiral catalyst with the aldehyde [27]. The α-amino radical is then oxidized by a hole of the valence band, yielding the iminium ion that releases catalyst and product.

39.3.2
α-Benzylation of Aldehydes

In the α-benzylation reaction a strong reductant was required to efficiently reduce benzyl bromides to the corresponding radical. *fac*-Ir(ppy)$_3$ (ppy = 2-phenylpyridine) was identified as a viable catalyst; it is used as a green triplet emitter in OLEDs since the excited state reduction potential, $E_{\mathrm{red}}[\mathrm{Ir(ppy)}_3{}^{4+}/{}^*\mathrm{Ir(ppy)}_3{}^{3+}]$, is calculated to be −1.73 V [5b]. The photocatalyst can readily accept a photon from weak fluorescent light to generate the strong reductant excited state *fac*-*Ir(ppy)$_3$ [$E_{½} = -1.73$ V versus saturated calomel electrode (SCE) in CH_3CN]. According to the mechanistic rationale, a SET from *fac*-*Ir(ppy)$_3$ to a suitable benzylic bromide gives rise to an aromatic radical anion that rapidly undergoes σ-bond cleavage to afford the bromide anion and an electrophilic benzyl radical. Within the same time frame, condensation of an aldehyde substrate with imidazolidinone catalyst **11** forms a highly π-nucleophilic enamine that then combines with the electron-deficient radical to enantioselectively forge the crucial homobenzylic center. Rapid oxidation of the resultant α-amino radical by *fac*-Ir(ppy)$_3^+$ ($E_{½}$ = 0.77 V versus SCE in CH_3CN) closes the redox cycle while regenerating the photocatalyst *fac*-Ir(ppy)$_3$. Various simple monoaryl and monoheteroaryl methylene halides were tested while the reaction is limited to electron-deficient aryl bromides (Scheme 39.20).

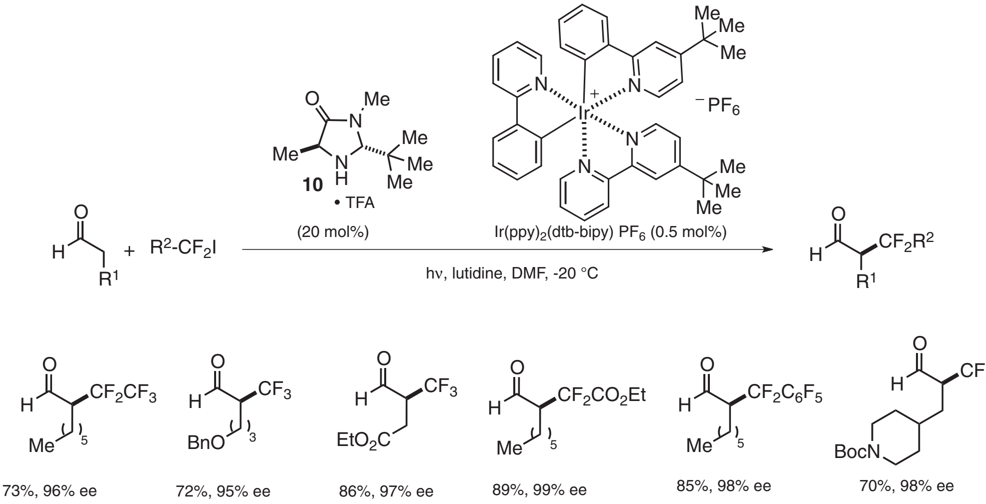


Scheme 39.20 Redox α-benzylation of aldehydes under organocatalytic conditions and the reaction scope.

Notably, however, the radical coupling is restricted to the most electron-deficient system. Electron-neutral benzylic halides did not readily undergo the initial reduction step, while the pyridinium radical is formed but does not couple with the enamine derived from catalyst **11**. Organocatalyst **11**, having trans benzyl and methyl stereo-elements of diminished steric demand, promotes long-lived enamine intermediates, and was also used in a higher concentration (20 mol%). This configuration thus increases the rate of the critical addition step.

39.3.3
α-Trifluoromethylation of Aldehydes

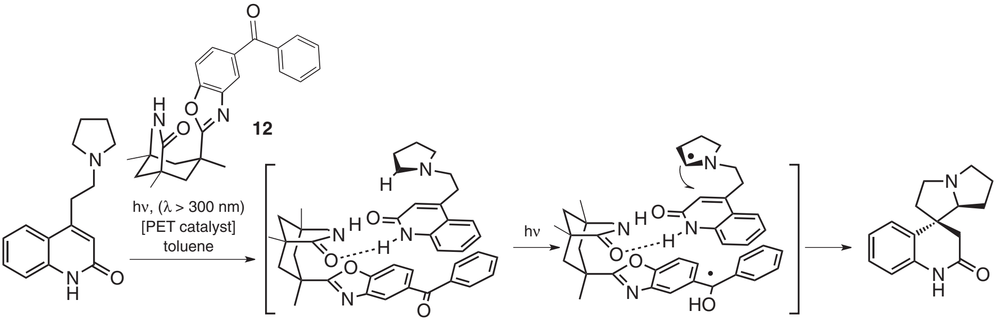
The installation of a trifluoromethyl group is particularly difficult at the late stage of a synthesis, in part because of the harsh protocols typically required for these reactions. Photoredox direct asymmetric α-trifluoromethylation and α-perfluoroalkylation of carbonyl compounds including ketones, esters, as well as aryls and heteroaryls without first preparing pre-functionalized or trifluoromethyl-containing substrates was developed upon irradiation, using in situ generated enolsilanes, silylketene acetals, and N,O-acetals [28a], or enamines [28b]. The radical stabilization energy of the CF_3 radical is 2.4 kcal mol^{-1}, which means that it is less stable than the CH_3 radical; thus the CF_3 radical is significantly more reactive than the CH_3 radical towards alkenes. For example, styrene reacts 440 times faster with the CF_3 radical than with the methyl radical. Factors governing the high reactivity are the pyramidalization of the CF_3 radical and polar effects in reactions with electron-rich alkenes. The asymmetric version of this transformation was realized by irradiation of the catalyst Ir(ppy)$_2$(dtb-bipy)$^+$, which undergoes a SET to CF_3I to give the CF_3 radical along with the oxidized catalyst (Scheme 39.21) [8f]. In a second catalytic cycle, organocatalyst **10**, added as a CF_3CO_2H salt (20 mol%), reacts with the starting aldehyde to give chiral enamine. Diastereoselective addition of the CF_3 radical onto the electron-rich enamine generates the adduct radical, which in turn is oxidized to iminium ion with the regeneration of the catalyst. Hydrolysis of the product eventually affords the fluorinated aldehyde, thereby regenerating the organocatalyst **10**.



Scheme 39.21 α-Trifluoromethylation of aldehydes and the reaction scope.

39.4
Photochemical Asymmetric Synthesis

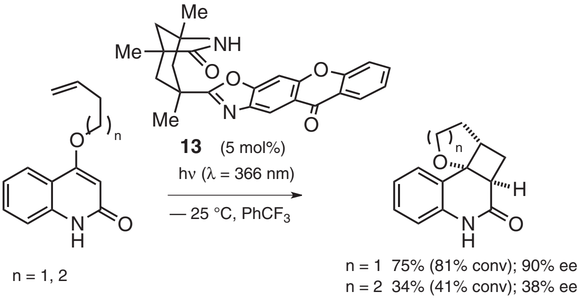
Photochemical asymmetric synthesis ("photochirogenesis") uses photoexcited short-lived, weakly interacting molecular states. Their short lifetimes makes it challenging to control electron transfer and subsequent product formation and asymmetric induction in particular [30]. Until recently the transfer of chiral information was restricted to photoreactions where the chirality transfer was assured by a stoichiometric amount of chiral auxiliaries or hosts [29–32]. Such systems were developed from cyclodextrins, clathrates, chirally modified zeolites, biomacromolecules, and proteins [29], and also from ionic liquids [31], rigid chiral complexing templates [32] and crystal lattices in which the substrate was oriented through hydrogen bonding or by local charges. Unfortunately, these chiral templates showed low turnover number (if any) in most cases. The use of chiral photosensitizers that can transfer energy or electrons, along with the chiral information, to a substrate is a novel strategy. The advantage of this method is that the reaction, and thus chirality transfer, occurs exclusively in the excited state. Control of the structure of the reaction product is more difficult, however, owing to the weak short-lived interactions in the excited state. A chiral organocatalyst family that combines significant rate acceleration by triplet energy transfer was developed and used for the enantioselective conjugate additions of α-amino alkyl radicals to enones. The chiral catalyst **12** (Scheme 39.22), used in 10 mol%, contains a photosensitizer component – benzophenone – and a group known as a Kemp triacid derivative, which uses two hydrogen bonds to attach to a specific substrate like a template [33]. The substrate–catalyst complex must form effectively to ensure that sensitization in this complex is faster than intermolecular sensitization. To avoid direct excitation of substrate the activation process works only selectively if there is little or no spectral overlap between substrate and catalyst in a wavelength region in which an excitation of the catalyst is possible with a given light source. The chiral sensitizer (i.e., the benzophenone moiety) induces a PET (photoinduced electron transfer) from the H-bonded substrate upon UV irradiation to the photoexcited catalyst by accepting an electron from the nitrogen of the bound organic substrate. In this complex the triplet energy of the sensitizer is significantly higher than the triplet energy of the substrate, allowing rapid energy transfer even at low temperature. Subsequent proton loss from the intermediate cation radical leads to an α-aminoalkyl radical (Scheme 39.22), which adds intramolecularly to C(4) of the quinolone. Importantly, the critical asymmetric bond-forming reaction is faster than the dissociation of the substrate from the catalyst, ensuring effective enantiotopic control of the chiral catalyst to the substrate. After the radical addition, back



Scheme 39.22 Mechanistic rationale of the asymmetric photoinduced electron transfer (PET)-catalyzed cyclization of the H-bonded substrate via formation of the radical intermediate.

electron transfer from the catalyst generates an enolate, which is eventually protonated to yield the products. The chiral catalyst serves thus as PET agent, and as a stereocontrolling device. The system allows obtainment of up to 70% ee, with a yield of 52–64% and turnover numbers of between 2.1 and 12.2.

A similar strategy was used [34] in the intramolecular [2+2]-photocycloaddition reactions of 4-substituted quinolones [35] in which xanthone-based organocatalyst **13** was preferred as sensitizer instead of the benzophenone **12** (Scheme 39.23). Chirality turnover was achieved with merely 5 mol% of catalyst, with enantioselectivities reaching or exceeding 90% ee for products after 1 h of irradiation at −25 °C. The reaction was more enantioselective with 4-(but-3-enyloxy)quinolone (*n* = 1), leading to a five-membered ring (90% ee with 5 mol% and 94% ee with 20 mol% catalyst) than the reaction of 4-(pent-4-enyloxy)quinolone (*n* = 2) leading to a six-membered ring, annelated to the cyclobutane. This difference in selectivity was attributed to the difference in reaction kinetics, as the former photocycloaddition was significantly faster, supporting the idea that the catalyst must host the substrate long enough to ensure efficient stereocontrol before dissociation. Conversion increased with increasing reaction time but isolation became troublesome owing to decomposition of the sensitizer.



Scheme 39.23 Asymmetric intramolecular [2+2]-photocycloaddition reactions of 4-substituted quinolones.

39.5
Conclusion

Electron-transfer-mediated asymmetric bond-forming reactions are novel additions to the organocatalytic arsenal. While non-asymmetric ET reactions are popping up regularly, the development of asymmetric methods seems to be taking place relatively slowly. Several elegant and previously elusive transformations have been found and developed, while the substrate scope remains a major issue. More detailed understanding of the reaction mechanisms may pave the way for more general applications.

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40
Organocatalytic Sigmatropic Reactions

Guillem Valero and Albert Moyano

40.1
Introduction

Rearrangement reactions involving carbon-to-carbon or carbon-to-heteroatom migrations often provide unique paths for the rapid assembly of synthetically challenging organic molecules [1, 2]. In most instances, rearrangements are concerted processes, going through highly ordered cyclic transition states, so that these reactions take place with high levels of regio- and stereoselectivity, and not only the atomic connectivity but also the spatial atomic arrangement of the resulting products can be efficiently controlled. Although the study of molecular rearrangements dates back to the beginnings of organic chemistry in the nineteenth century, in the past two decades there has been an increasingly growing interest in stereocontrolled variants of sigmatropic rearrangements. As has happened with other synthetically useful methods such as cycloaddition or cyclization reactions, current investigations have led to the development of chiral catalysts that enable the use of rearrangements for the efficient preparation, in a diastereo-and enantioselective fashion, of biologically active natural products or of medicinally important chiral compounds. In comparison with the extensive use of asymmetric organocatalysis based on the aldol [3], Mannich [4], Diels-Alder [5], Michael reactions [6], and other chemical transformations [7], progress in the development of organocatalytically enantiocontrolled rearrangement reactions has been relatively slow. Thus, the first review devoted to the application of asymmetric organocatalysis to sigmatropic rearrangements was published in 2010 [8]. In this chapter we survey the most relevant instances of asymmetric organocatalytic sigmatropic reactions, covering the literature until the beginning of 2012. Note that in this chapter we will adopt the more general IUPAC definition of a sigmatropic reaction as a molecular rearrangement that involves both the creation of a new σ-bond between atoms previously not directly linked and the breaking of an existing σ-bond, so that we will deal with both concerted (pericyclic) and stepwise sigmatropic rearrangements.

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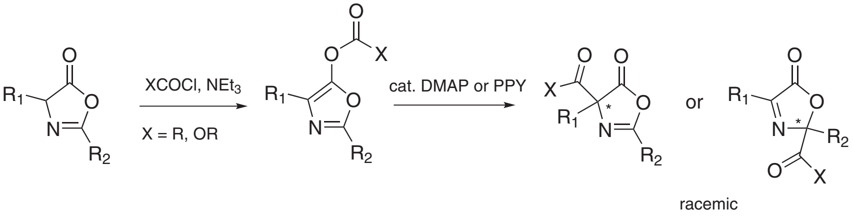
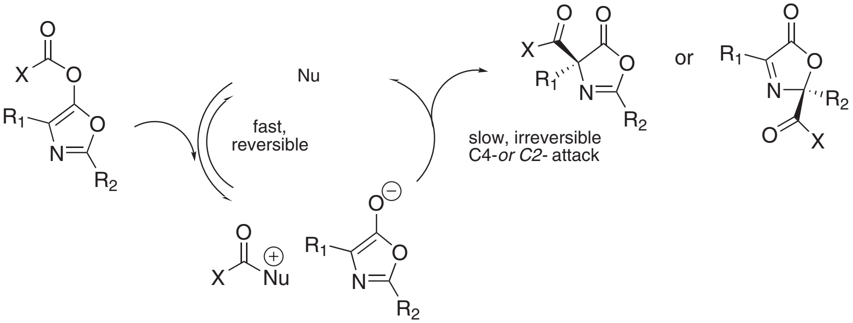
40.2
Steglich and Related Rearrangements

The rearrangement of *O*-acylated azlactones (or of oxazolyl carbonates) to a *C*-acyl- (or to a *C*-carboxy) azlactone takes place easily at room temperature in the presence of catalytic amounts of 4-(dimethylamino)pyridine (DMAP) or of 4-(1-pyrrolidinyl) pyridine (PPY), as first disclosed by Steglich and Höfle in 1969 (Scheme 40.1) [9]. Although the product is usually a 4-acyl- (or a 4-alkoxycarbonyl)azlactone, if the R_2 substituent is electron-donating the rearrangement at C2 can take place.



Scheme 40.1 Steglich rearrangement of *O*-acylated azlactones.

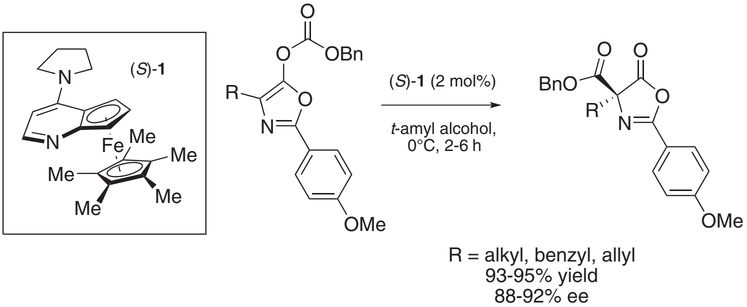
The commonly accepted mechanism for the Steglich rearrangement, depicted in Scheme 40.2, involves a fast and reversible attack of the nucleophilic catalyst to the acyl of alkoxycarbonyl group, leading to an ion pair that in a slow irreversible step leads to the formation of the C4- or C2-substituted azlactone. If the nucleophile is chiral, the acyl cation can discriminate between the two enantiotopic faces of the azlactone enolate, affording enantiomerically enriched products.



Scheme 40.2 Mechanism of the Steglich rearrangement.

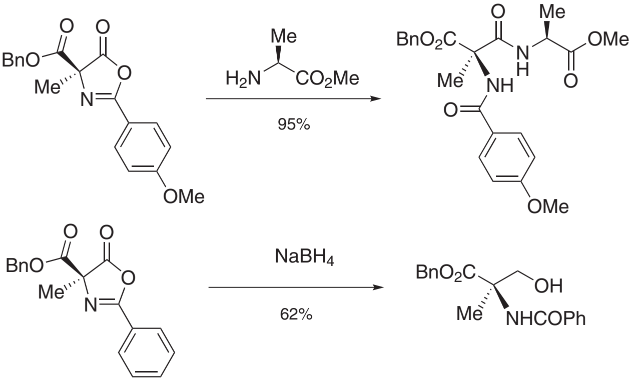
In 1998, Ruble and Fu [10] reported on the use of ferrocene-derived chiral 4-aminopyridines [11] in the Steglich rearrangement of 2-aryl-4-alkyloxazolones (Scheme 40.3). After the systematic optimization of several reaction parameters, the authors found that the planar-chiral ferrocene derivative (*S*)-**1** catalyzed the rearrangement of an array of *O*-benzyloxycarbonyl azlactones with total

C4-regioselectivity, with high enantioselectivities (88–92% ee) and in excellent yields (93–95%).



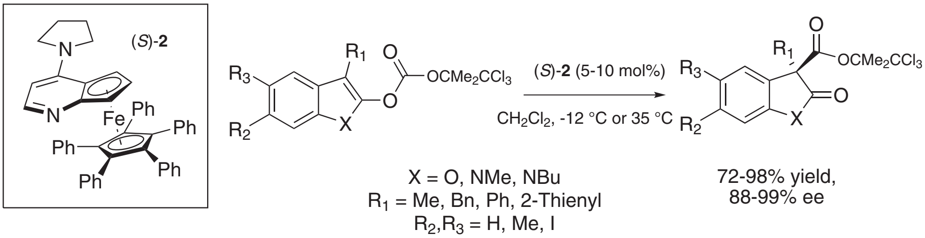
Scheme 40.3 Enantioselective Steglich rearrangement of *O*-carbonylated azlactones catalyzed by a chiral 4-(pyrrolidino)pyridine (PPY) derivative.

These rearranged azlactones can be easily converted into quaternary α-alkylated α-amino acid derivatives, either by ring opening with a primary amine or by reduction with sodium borohydride (Scheme 40.4). X-Ray diffraction analysis of an amide derived from a chiral amine allowed assignment of the absolute configuration of the rearrangement products as that arising from electrophilic attack at the C4-*Si*-face.



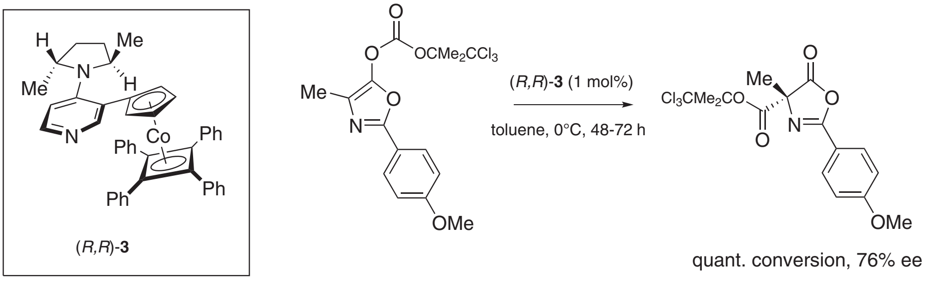
Scheme 40.4 Conversion of the Steglich rearrangement products into quaternary α-amino acid derivatives.

Subsequently, Hills and Fu [12] reported that the related rearrangements of *O*-carbonylated benzofuranones [13] and oxindoles were efficiently catalyzed, and with excellent enantioselectivity, by the more sterically hindered 4-(pyrrolidino) pyridine derivative (*S*)-**2** (Scheme 40.5). X-Ray diffraction analysis of a rearranged oxindole showed that the asymmetric sense of induction of this rearrangement was the same as that of the (*S*)-**1** catalyzed Steglich rearrangement. The mechanisms of both types of rearrangements are probably very similar, and in fact the authors were able to obtain a low-resolution X-ray crystal structure of an ion pair derived from catalyst (*S*)-**2** and an *O*-acylated benzofuranone.



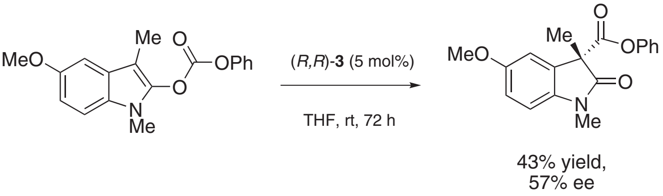
Scheme 40.5 Enantioselective rearrangement of *O*-carbonylated benzofuranones and oxindoles catalyzed by a chiral 4-(pyrrolidino)pyridine (PPY) derivative.

Synthesis of the planar chiral ferrocene derivatives **1** and **2** is rather lengthy and requires a subsequent chromatographic resolution to obtain the enantiopure compound. In an attempt to overcome this limitation, Richards and coworkers [14] developed the central-chiral cobaltocene-4-(pyrrolidino)pyridine nucleophilic catalyst (*R,R*)-**3**, which is available in three steps from (*S,S*)-hexane-2,3-diol. The rationale for the design of this catalyst relied on the stereochemistry relay of an enantiopure C_2-symmetric pyrrolidine through the pyridine nitrogen by use of a bulky metallocene moiety attached at C3. Although this metallocene showed good catalytic activity, its application to the Steglich rearrangement gave only moderate enantioselectivities (Scheme 40.6). The absolute configuration [14] of the rearranged products, determined by comparison of the optical rotation of the same compound previously obtained by Fu, indicated that Richards' catalyst (*R,R*)-**3** favored the alkoxycarbonylation at the C4 *Re*-face of the azlactone anion.



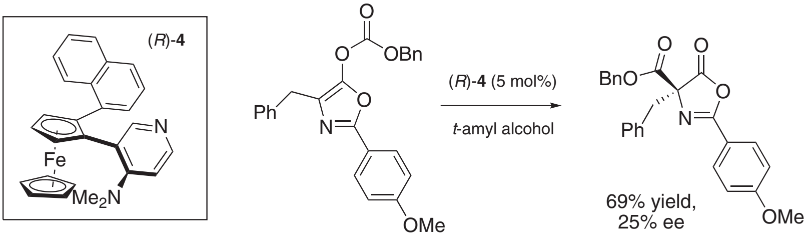
Scheme 40.6 Enantioselective Steglich rearrangement with catalyst (*R,R*)-**3**.

Richards' cobaltocene has also been used in the rearrangement of oxindole-derived enol carbonates, although with poor yields and enantioselectivities (Scheme 40.7) [15].



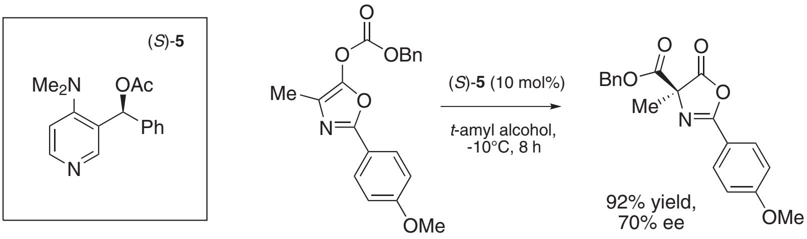
Scheme 40.7 Enantioselective rearrangement of oxindole-derived enol carbonate.

Compound (*S*)-**4**, devised by Johanssen and coworkers as a new type of ferrocene-based planar chiral ferrocene-based DMAP analog and obtained in six steps from enantiopure Kagan's ferrocene sulfoxide, gave only marginal enantioselectivities in the Steglich rearrangement of an *O*-carbonylated oxazolone (Scheme 40.8) [16].



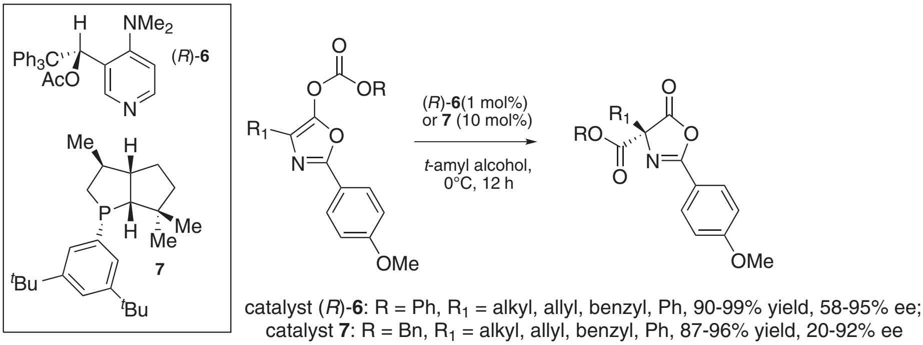
Scheme 40.8 Enantioselective Steglich rearrangement catalyzed by ferrocene (*R*)-**4**.

Purely organic chiral DMAP or PPY derivatives have also been tested as catalysts for the asymmetric Steglich rearrangement. Gotor and coworkers developed an enantioselective synthesis of DMAP analogues through a chemical oxidation–enzymatic reduction sequence [17]. The best of the catalysts tested by Gotor, the acetate (*S*)-**5**, gave moderately good enantioselectivity in the rearrangement of an oxazolone carbonate (Scheme 40.9).



Scheme 40.9 Enantioselective Steglich rearrangement catalyzed by a chiral 3-substituted DMAP.

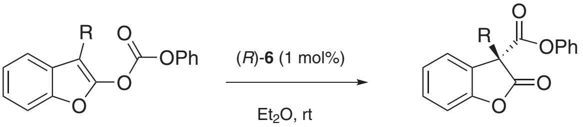
Better results were obtained by Vedejs and coworkers with the 3-substituted 4-(dimethylamino)pyridine catalyst (*R*)-**6** [18]. The chiral phosphabicyclooctane **7** was also studied by Vedejs' group and gave somewhat inferior enantioselectivities (Scheme 40.10).



catalyst (R)-**6**: R = Ph, R_1 = alkyl, allyl, benzyl, Ph, 90-99% yield, 58-95% ee;
catalyst **7**: R = Bn, R_1 = alkyl, allyl, benzyl, Ph, 87-96% yield, 20-92% ee

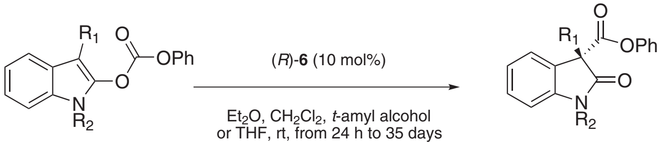
Scheme 40.10 Enantioselective Steglich rearrangement of *O*-carbonylated azlactones with Vedejs' catalysts **6** and **7**.

The absolute configuration of the rearranged products was again ascertained by determining the sign of optical rotation of one compound previously obtained by Fu [10]. Catalyst **6** was successfully tested in the rearrangement of *O*-carbonylated benzofuranones (Scheme 40.11) and of *O*-carbonylated oxindoles (Scheme 40.12), although for this last class of compounds the enantioselectivities were lower than those recorded by Hills and Fu [12].



R = alkyl, benzyl; 88-97% yield, 92-93% ee

Scheme 40.11 Enantioselective rearrangement of *O*-carbonylated benzofuranones with catalyst (*R*)-**6**.



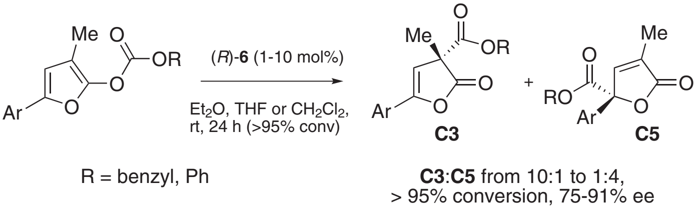
R1
O
OPh
O
N
R2
(R)-6 (10 mol%)
Et2O, CH2Cl2, t-amyl alcohol
or THF, rt, from 24 h to 35 days
O
R1
OPh
O
N
R2

R_1 = Me, Ph, R_2 = alkyl,
aryl, benzyl, alkoxycarbonyl

> 95% conversion, 18-90% ee

Scheme 40.12 Enantioselective rearrangement of *O*-carbonylated oxindoles with catalyst (*R*)-**6**.

Vedejs' group [18] also investigated the rearrangement of 3-methyl-5-arylfuran enol carbonates (Scheme 40.13); for these substrates, competition between alkoxycarbonylation at C3 (1,3-rearrangement) and at C5 (1,5-rearrangement) was observed [19]. The nature of the aromatic substituent appears to determine the regiochemical outcome of the reaction: electron-donating substituents in the C5-phenyl group favor the formation of the C3-rearranged product, while electron-withdrawing ones increase the amount of C5-rearranged product. In both instances, the sense of asymmetric induction with catalyst (*R*)-**6** is the same, and coherent with that observed with azlactones, benzofuranones, and oxindole derivatives.



Scheme 40.13 3-Methyl-5-arylfuran enol carbonate rearrangement with catalyst (*R*)-**6**.

Vedejs *et al.*, on the basis of both DFT calculations and of X-ray diffraction analysis of compound **6**, proposed a qualitative model for the stereochemical induction observed with this catalyst [18b]. These authors conjectured that in the transition state of the Steglich and related rearrangements, to minimize the steric interactions, the endocyclic oxygen of the azlactone is oriented towards the acetoxy group and that the C4-substituent is placed between the two oxygens of the phenoxycarbonyl group (Figure 40.1). This model would account for the preferred C4 *Re*-face attack observed with catalyst (*R*)-**6**.[1]

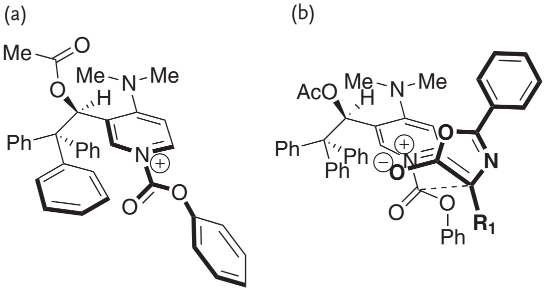


Figure 40.1 (a) Preferred conformation of the *N*-phenoxycarbonyl cation derived from Vedejs' catalyst (*R*)-**6**; (b) qualitative model for stereochemical induction in the Steglich rearrangement with catalyst (*R*)-**6**.

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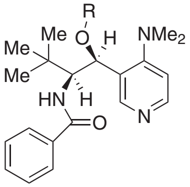
[1] For an extension of this model to Fu's catalysts, see Reference [3].

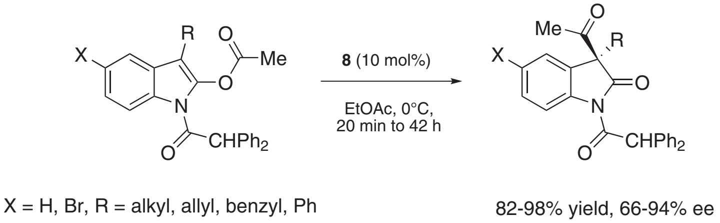


8 (R = Ac)
9 (R = Bn)

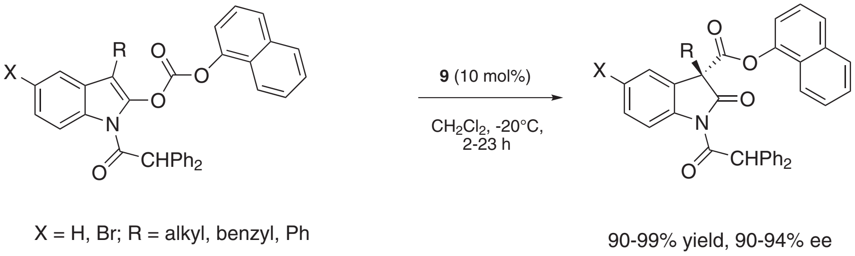
Figure 40.2 Vedejs' second-generation chiral DMAP analogs AcOLeDMAP (**8**) and BnOLeDMAP (**9**).

Subsequently, Vedejs and coworkers [20] uncovered a new class of chiral 4-(dimethylamino)pyridines. These compounds, named AcOLeDMAP (**8**) and BnOLeDMAP (**9**), were designed to favor a specific C3-side chain conformer (Figure 40.2); they can be easily obtained from (*S*)-*tert*-leucinol.

Compound **8** was a good catalyst for the rearrangement of indolyl *O*-acetates, a class of substrates in which **6** had afforded only marginal enantioselectivities (Scheme 40.14). The absolute configuration of the rearranged products showed that this catalyst exhibited a stereochemical induction opposite to that of the first-generation DMAP derivative (*R*)-**6**. When compound **9**, differing only in the nature of the alkoxy group, was used to catalyze the rearrangement of indolyl *O*-carbonates, oxindole products having the opposite configuration were obtained, with good enantiomeric purities (Scheme 40.15).

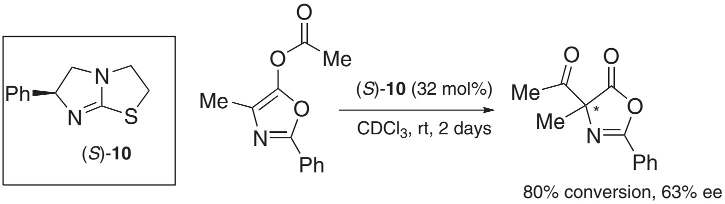


Scheme 40.14 Enantioselective rearrangement of *O*-acylated oxindoles with catalyst **8**.



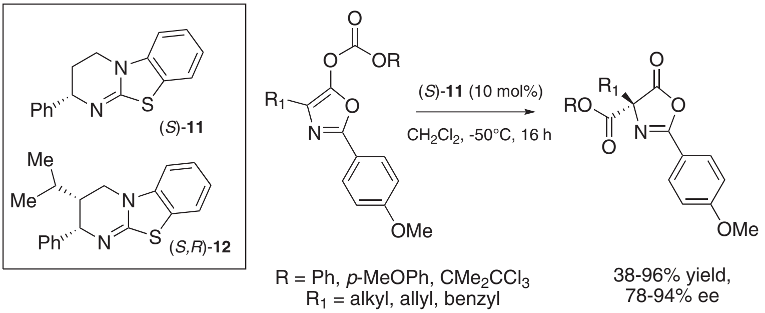
Scheme 40.15 Enantioselective rearrangement of *O*-carbonylated oxindoles with catalyst **9**.

The usefulness of chiral isothioureas as catalysts for the Steglich rearrangement was demonstrated for the first time in 2007 by Dietz and Gröger. [21]. The asymmetric Steglich rearrangement of *O*-acylated azlactones gave very low enantioselectivities (up to 25% ee) when catalyzed by Fu's planar chiral ferrocene derivative (*S*)-**1**; on the other hand, the readily available chiral bicyclic isothiourea (*S*)-**10** [(−)-tetramisole] afforded the rearrangement product in 63% ee, although even with large amounts of the catalyst (32 mol%) the reaction was very slow (Scheme 40.16). Subsequently, the same authors reported on the use of this methodology for the asymmetric synthesis of all stereoisomers of α-methylthreonine [22].



Scheme 40.16 Asymmetric acyl migration in the Steglich rearrangement.

Another chiral isothiourea, HBTM (*S*)-**11**, previously developed by Birman and Li for the kinetic resolution of aryl cycloalkanols [23], was found by A.D. Smith and coworkers [24] to give excellent yields and enantioselectivities in the Steglich rearrangement of oxazolyl carbonates (Scheme 40.17). The related catalyst (*S,R*)-**12** gave very similar results.



Scheme 40.17 Enantioselective Steglich rearrangement of *O*-carbonylated azlactones catalyzed by a chiral isothiourea.

The absolute configuration of the rearranged products resulted from a C4 *Re* face attack to the oxazolone anion. The authors, to explain this stereochemical outcome, performed DFT calculations on both the preferred conformation of the *N*-phenoxycarbonyl cation derived from (*S*)-**11** and on the transition state for the

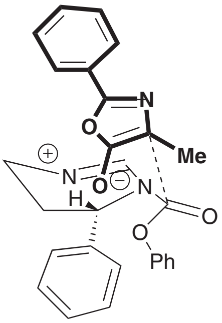
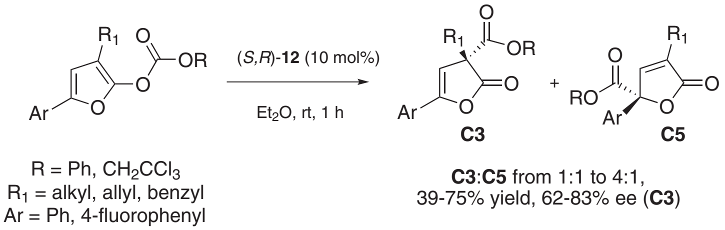


Figure 40.3 Smith's transition state model for the Steglich rearrangement catalyzed by isothiourea (*S*)-**11**.

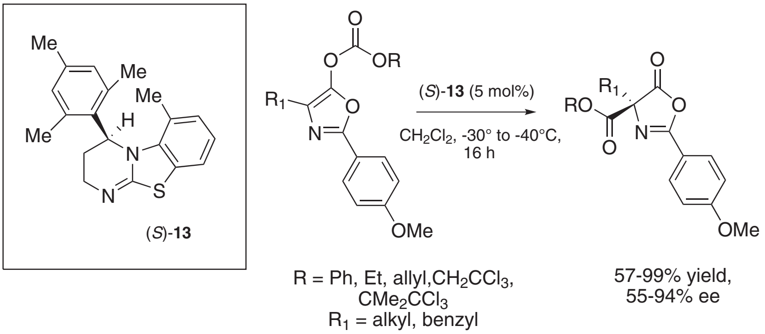
carbonyl transfer, and found that the lowest energy transition state was in fact that leading to the observed enantiomers (Figure 40.3). This transition state appears to be stabilized by CH–O interactions between the enolate and the cation, as well as by electrostatic interactions [24]. The transition state leading to the opposite enantiomer was ca. 4.0 kcal mol^{-1} less stable.

Catalyst (*S,R*)-**12** was also tested in the asymmetric rearrangement of furanyl carbonates (Scheme 40.18). As previously observed by Vedejs *et al.* [18], the reaction gave a regioisomeric mixture of rearranged products, but in general the C3-regioisomer was the major one. Both the yields and the enantiomeric excess were moderate or good [25]. The stereochemical outcome of the reaction was rationalized by the authors by a transition state model similar to that depicted in Figure 40.3.



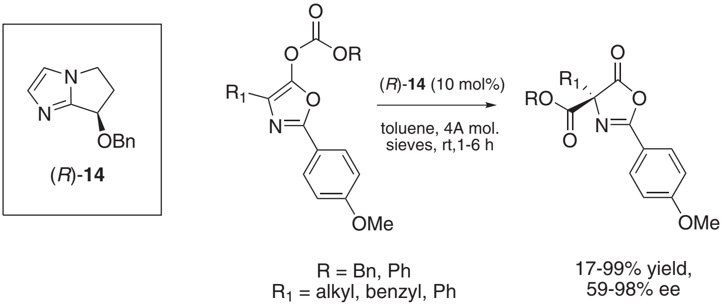
Scheme 40.18 Isothiourea **12** promoted *O*- to *C*-carbonyl rearrangement of furanyl carbonates.

The structurally related isothiourea (*S*)-**13** was synthesized by Okamoto and coworkers, and used as a catalyst in the Steglich rearrangement of oxazolyl carbonates [26]. As shown in Scheme 40.19, yields and enantioselectivities ranged from good to excellent. The same compound can also catalyze the *O*- to *C*-carbonyl rearrangement of benzofuranone and oxindole-derived carbonates, but with poor enantioselectivity. MM2 calculations again give support to Smith's transition state model [24].


(S)-13
(S)-13 (5 mol%)
CH2Cl2, -30° to -40°C, 16 h
R = Ph, Et, allyl, CH2CCl3, CMe2CCl3
R1 = alkyl, benzyl
57-99% yield, 55-94% ee

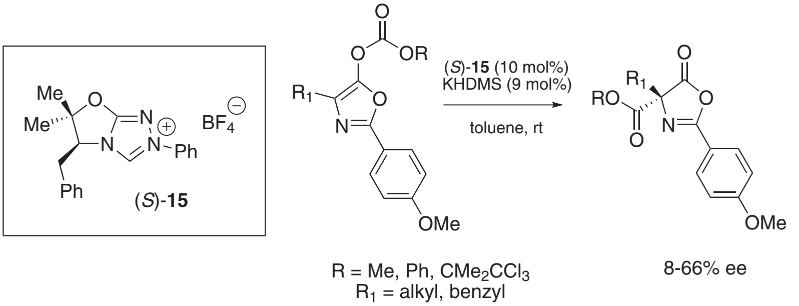
Scheme 40.19 Isothiourea **13** promoted Steglich rearrangement of oxazolyl carbonates.

Zhang and coworkers have designed a new structural type of nitrogen-based nucleophilic catalyst, based on chiral bicyclic imidazoles. Compound (*R*)-**14** was a good catalyst for the Steglich rearrangement of azlactone carbonates (Scheme 40.20) [27]. A limitation of this methodology is the rather difficult preparation of the catalyst in enantiopure form (low yield resolution of the racemic with tartaric acid or by preparative HPLC).



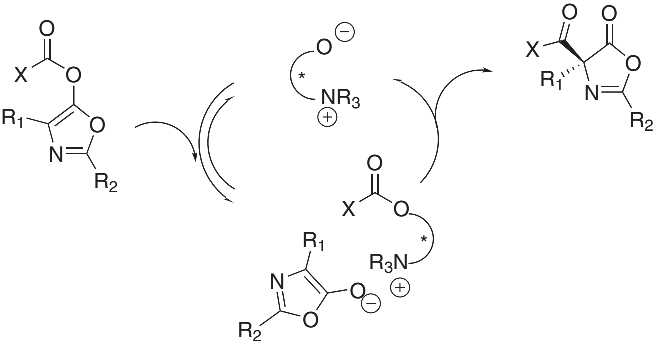
Scheme 40.20 Imidazole **14** promoted Steglich rearrangement of oxazolyl carbonates.

Smith and coworkers have investigated the ability of chiral N-heterocyclic carbenes (NHCs) to promote the asymmetric Steglich rearrangement [28]. After an extensive study, it was found that the carbene derived from the oxazoline-triazolium salt **15** was the best catalyst (Scheme 40.21).



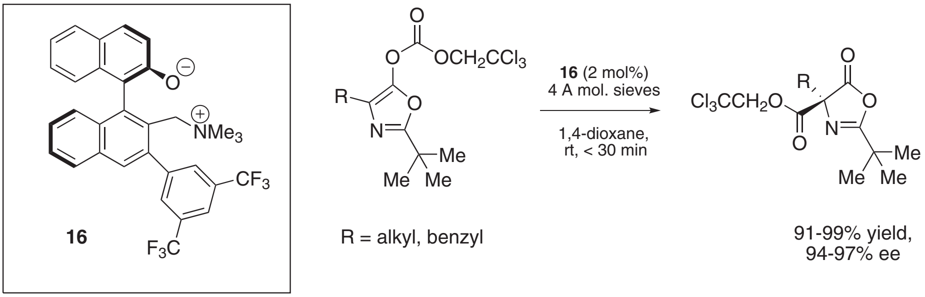
Scheme 40.21 Asymmetric Steglich rearrangement catalyzed by a N-heterocyclic carbene.

In 2010, Ooi and coworkers proposed the use of chiral ammonium betaines as asymmetric ionic nucleophilic catalysts [29]. They reasoned that an intramolecular alkoxonium salt could be an efficient catalyst for the Steglich rearrangement – since the alkoxide anion would displace the carbonyl substituent in the intermediate ion pair the ammonium cation would be engaged in an ionic interaction with the azlactone anion, enhancing both the rate and the stereoselectivity of the acyl transfer step (Scheme 40.22).



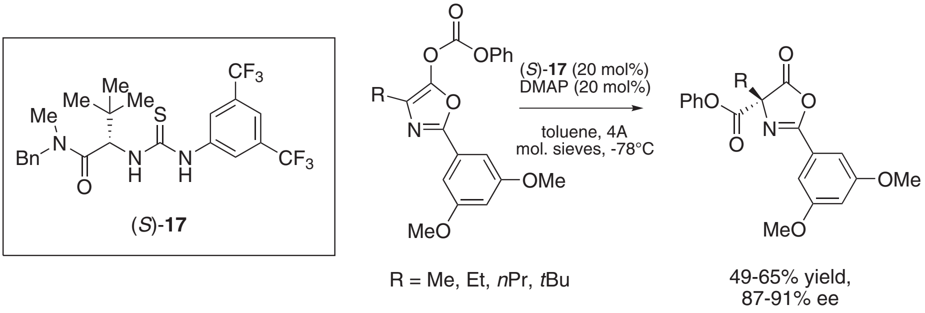
Scheme 40.22 Ooi's working hypothesis for the Steglich rearrangement with an onium alkoxide as catalyst.

In accordance with this working hypothesis, the chiral ammonium betaine **16** proved to be a highly efficient catalyst for the *O*- to *C*-rearrangement of azlactone carbonates (Scheme 40.23).



Scheme 40.23 Asymmetric Steglich rearrangement catalyzed by a chiral ammonium betaine.

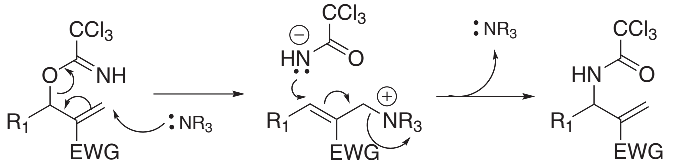
Seidel and coworkers have developed a new concept for asymmetric nucleophilic catalysis, in which an achiral nucleophile is used in combination with a chiral hydrogen-bonding catalyst. The application of this concept to the Steglich rearrangement implied the use of simple DMAP as the achiral nucleophile and of the thiourea **17** as the chiral hydrogen-bond donor co-catalyst (Scheme 40.24) [30].



Scheme 40.24 Dual-catalysis approach to the asymmetric Steglich rearrangement.

40.3
1,3-Sigmatropic Rearrangements

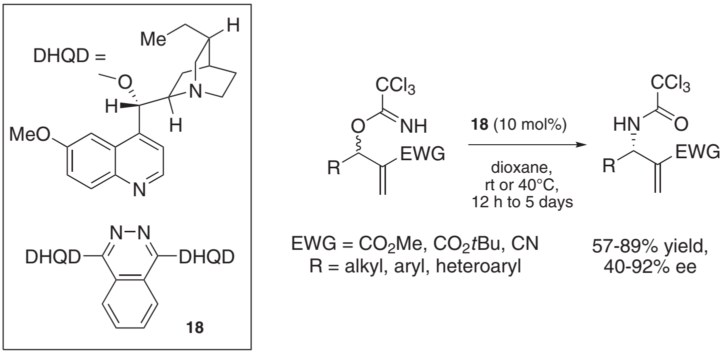
The first organocatalyzed asymmetric 1,3-sigmatropic *O*- to *N*-rearrangement was disclosed in 2008 by Jørgensen and coworkers [31]. These authors studied, initially, the 1,3-sigmatropic rearrangement of trichloroacetimidates derived from Morita–Baylis–Hillman (MBH) adducts to allylic amides, a tertiary amine-catalyzed variant of the Overman rearrangement [32] and whose mechanism is believed to involve a S_N2' displacement of the trichloroacetimidate (facilitated by the presence of an electron-withdrawing group at the C2 position of the allylic moiety), followed by a subsequent S_N2' attack of the nitrogen nucleophile of the anionic trichloroacetamide and release of the tertiary amine catalyst (Scheme 40.25).



EWG = electron-withdrawing group

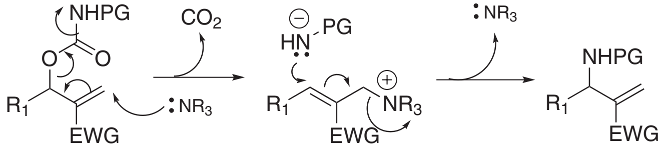
Scheme 40.25 Mechanism of the tertiary amine-catalyzed rearrangement of *O*-allylic trichloroacetimidates to allylic amides.

Suitable chiral tertiary amine catalysts for this rearrangement are cinchona-alkaloid derivatives, and Jørgensen *et al.* found that the best conditions involved the use of the well-known Sharpless' $[DHQD]_2PHAL$ ligand **18** and dioxane as solvent (Scheme 40.26).



Scheme 40.26 Organocatalytic asymmetric rearrangement of *O*-allylic trichloroacetimidates.

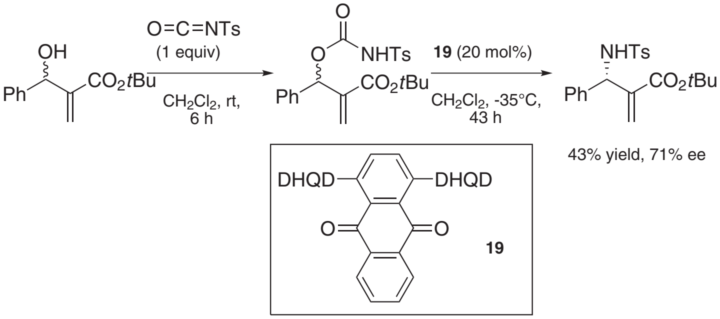
A related 1,3-rearrangement, also studied by Jørgensen, is the decarboxylative rearrangement of *O*-carbamates derived from MBH adducts, an amine-catalyzed reaction that also takes place via a domino S_N2'–S_N2' mechanism (Scheme 40.27).



Scheme 40.27 Tertiary amine-catalyzed rearrangement of *O*-allylic carbamates to allylic amines.

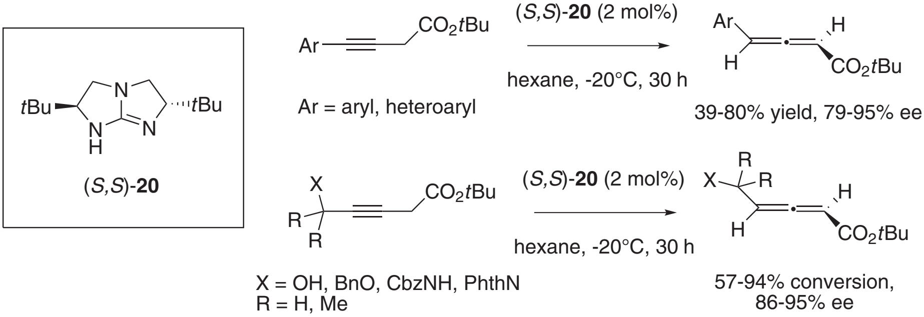
From the experimental point of view, this rearrangement was best performed when coupled with *in situ* generation of the substrates from MBH adducts, using a sulfonamide as the amine-protecting group and Sharpless' $[DHQD]_2AQN$

ligand **19** as catalyst (Scheme 40.28). The absolute configuration of the rearranged amines was ascertained by chemical correlation, and the stereochemical sense of induction was found to be the same as that of the rearrangement of allylic trichloroacetimidates.



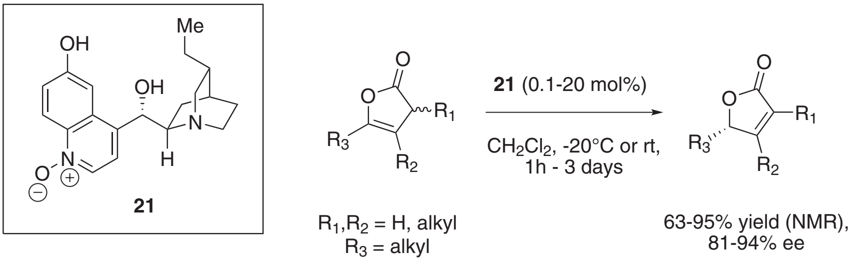
Scheme 40.28 Asymmetric organocatalytic rearrangement of an *O*-allylic carbamate to an allylic amine with *in situ* generation of the substrate.

In 2009, Tan and coworkers reported that the chiral bicyclic guanidine (*S,S*)-**20** was able to catalyze the enantioselective isomerization of 3-alkynoates to chiral allenoates in what (formally) constitutes a 1,3-hydrogen sigmatropic rearrangement (Scheme 40.29) [33]. The reaction took place in hexane at low temperature with high enantioselectivities, but conversions were not complete.

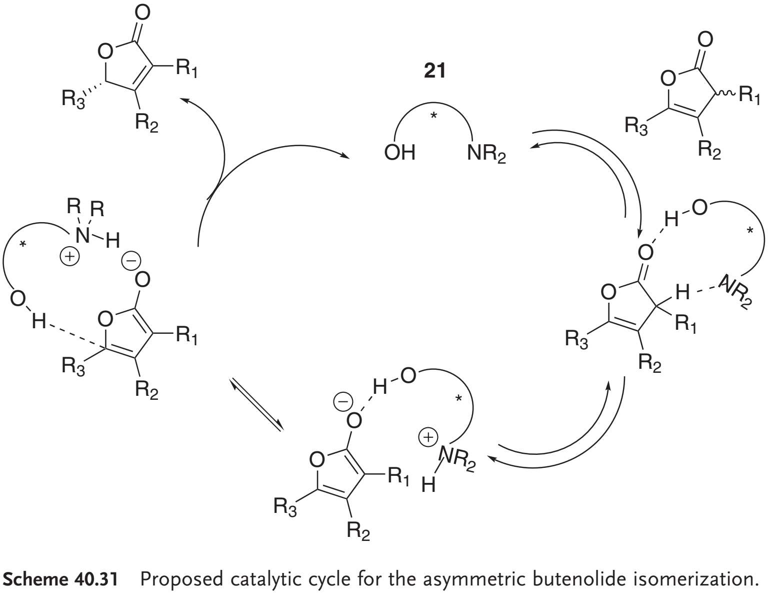


Scheme 40.29 Guanidine-catalyzed asymmetric isomerization of 3-alkynoates to allenoates.

A subsequent theoretical study of this process by Hu and coworkers [34], using DFT theory at the B3LYP/6-31+G(d,p) level, concluded that the isomerization reaction includes two hydrogen-transfer steps; the first one involves proton transfer from the C2 carbon of the alkynoate to the guanidine, and in the second one a proton is transferred from the catalyst to the C4 carbon of the substrate. The calculations predict that deprotonation of the substrate may be the rate-determining step, but that the stereochemistry of the product is governed by the relative energies of the transition states for the second step. Another double bond isomerization reaction, which consists of a formal 1,3-hydrogen rearrangement but which probably takes place via a deprotonation–deprotonation pathway, is the organocatalytic asymmetric isomerization of butenolides reported by Deng and coworkers [35]. These authors have found that the dihydroquinidine derivative **21** catalyzes the double bond isomerization of a series of achiral or racemic γ-substituted-β,γ-unsaturated butenolides to the chiral α,β-unsaturated regioisomers with excellent levels of stereoselectivity (Scheme 40.30). The proposed mechanism implies the Cα-deprotonation of the butenolide, followed by rate-limiting Cγ-reprotonation of the butenolide anion (Scheme 40.31).



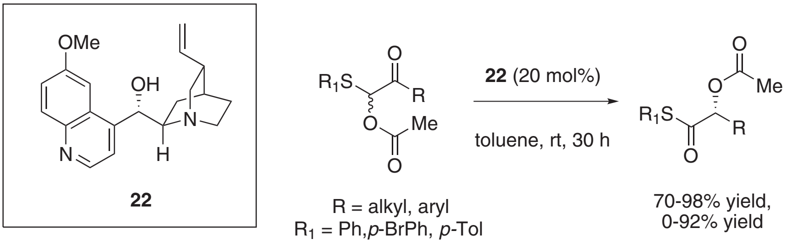
Scheme 40.30 Asymmetric olefin isomerization of butenolides via proton-transfer organocatalysis.



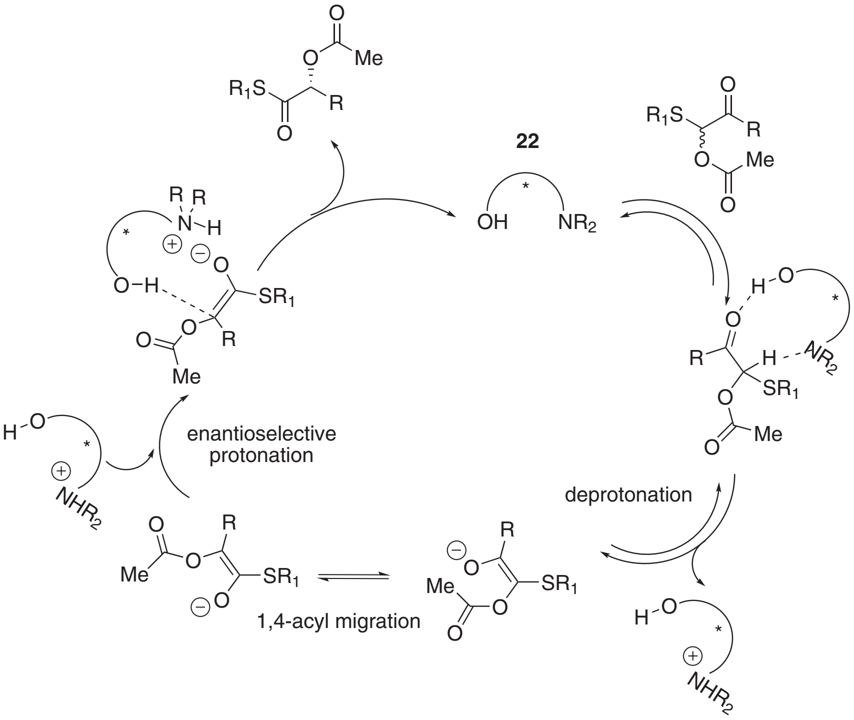
Scheme 40.31 Proposed catalytic cycle for the asymmetric butenolide isomerization.

40.4
1,4-Sigmatropic Rearrangements

The highly enantioselective organocatalytic rearrangement of racemic α-acetoxy-β-ketosulfides (compounds that are easily obtained by Pummerer rearrangement of β-ketosulfoxides) to α-acetoxythioesters was reported by Frongia and coworkers in 2010 [36]. The process, which is formally a 1,4-*O,O* rearrangement of an acetyl group, can be conveniently catalyzed by quinidine **22** (Scheme 40.32). The proposed catalytic cycle, depicted in Scheme 40.33, involves the deprotonation of the



Scheme 40.32 Quinidine-catalyzed rearrangement of α-acetoxy-β-ketosulfides to α-acetoxythioesters.



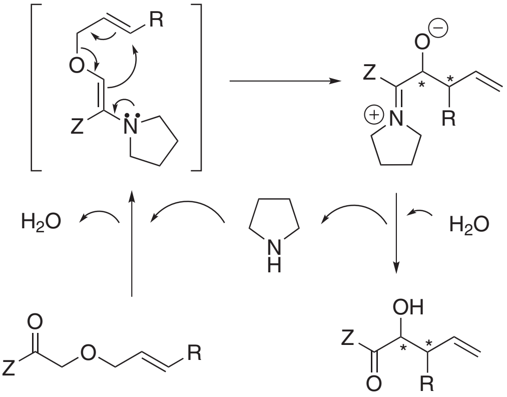
Scheme 40.33 Proposed mechanistic cycle for the rearrangement of α-acetoxy-β-ketosulfides.

α-acyloxy-β-ketosulfide by quinidine, furnishing a transient enolate species that undergoes acyl migration to another transient enolate that, in turn, undergoes an asymmetric proton transfer from the protonated quinidine, affording the α-acyloxy-thioester product in enantiomerically enriched form and releasing the catalyst back into the cycle.

More recently, the same authors uncovered the analogous rearrangement of α-acetoxy-β-iminosulfides, leading to α-acetamido-thioester s with moderate yields and enantioselectivities [37].

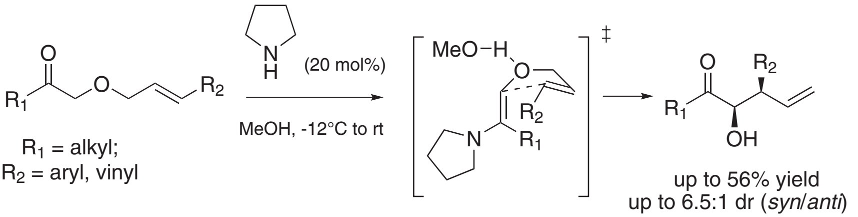
40.5
2,3-Sigmatropic Rearrangements

The 2,3-Wittig rearrangement is a synthetically useful reaction for which catalytic methods are scarce [38]. In 2006, Gaunt and coworkers [39] endeavored to develop an organocatalytic version of this rearrangement, based on enamine catalysis (Scheme 40.34).



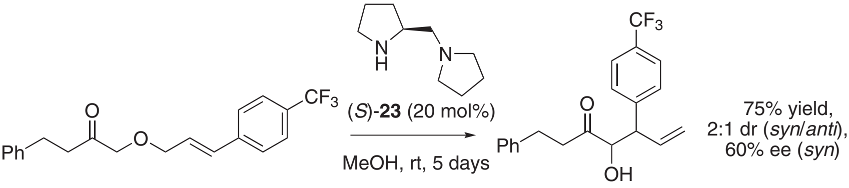
Scheme 40.34 Organocatalytic [2, 3] Wittig rearrangement.

These authors found that pyrrolidine was indeed able to catalyze the 2,3-Wittig rearrangement of several α-allyloxy methyl ketones with good yields and moderate to good diastereoselectivities (Scheme 40.35). The fact that the major diastereomer had a 1,2-*syn* relative configuration was explained by assuming that the rearrangement proceeded via an envelope *syn* transition state.



Scheme 40.35 Racemic organocatalytic 2,3-Wittig rearrangement of α-allyloxy methyl ketones.

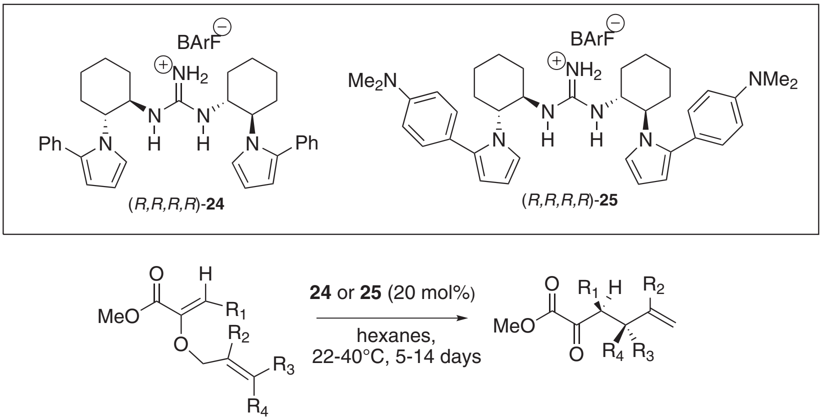
The use of chiral secondary amines to develop an asymmetric organocatalytic process proved, however, to be rather challenging, and the authors could only provide a single example, catalyzed by the L-proline derivative **23**, affording a moderate 60% ee of the major diastereomer of the rearranged product, of unknown absolute configuration (Scheme 40.36).



Scheme 40.36 Organocatalytic asymmetric 2,3-Wittig rearrangement.

40.6
3,3-Sigmatropic Rearrangements

The aliphatic Claisen rearrangement is arguably one of the most synthetically useful among sigmatropic processes, due both to its efficient construction of carbon–carbon bonds and to its exquisite degree of stereocontrol in the resulting stereogenic carbon atoms and double bonds. However, this reaction has proven to be extremely resistant to asymmetric catalysis [2, 40], probably due to the poor coordinating ability of the ether oxygen. In 1992, Severance and Jorgensen [41] used quantum mechanical calculations to explain the accelerating effect of protic solvents or of Brønsted acids on the rate of the Claisen rearrangement. They were able to propose a model for the aqueous acceleration of the reaction involving hydrogen-bond interactions between two water molecules and the ether oxygen in the transition state structure, and suggested a catalyst design incorporating two hydrogen-bond-donating sites; however, subsequent experimental studies using either ureas [42] or thioureas [43] found only modest rate accelerations even when these additives were present in stoichiometric amounts. Uyeda and Jacobsen reasoned that stronger hydrogen-bond donors were required, and in 2008 they disclosed that an achiral *N,N′*-diphenylguanidinium salt induced significant rate enhancements in the Claisen rearrangement of several allyl vinyl ethers [44]. After extensive optimization of the structures of both the substrate and the catalyst, and of the reaction conditions, they were also able to show that excellent yields and enantioselectivities could be achieved in the 3,3-rearrangement of allyl vinyl ethers bearing a methoxycarbonyl substituent at C2 when using 20 mol% of the chiral guanidinium salt **24** (Scheme 40.37).



catalyst **24**:	R_1 = alkyl; R_2 = H, Me; R_3 = H, alkyl, allyl, Ph; R_4 = H, Me	73-92% yield, 81-96% ee
catalyst **25**:	R_1 = alkyl; R_2 = H; R_3 = H, alkyl; R_4 = H, alkyl	81-93% yield, 84-88% ee (75-92% yield and 73-84% ee with **24**)

Scheme 40.37 Enantioselective Claisen rearrangement catalyzed by chiral guanidinium salts.

The starting ester-substituted allyl vinyl ethers can be prepared from the corresponding α-keto acids, with complete selectivity for the (*Z*)-isomer, by a two-step procedure involving *O*-alkylation with an allylic mesylate and treatment with diazomethane. Di- and tri-substituted compounds rearranged with high selectivity (>19 : 1 dr) for the major diastereomer predicted by a six-membered chair-like transition state. Quaternary stereocenters were formed with good stereocontrol. Compounds with more sterically hindered isopropyl and isobutyl R_2 substituents were obtained only with moderate enantioselectivities (73% and 69% ee, respectively). The mechanism of this organocatalytic rearrangement was investigated by the same authors both by experimental (kinetics, catalyst–substrate binding constants) and by theoretical [DFT calculations at the B3LYP/6-31G(d) level] methods [45]. These studies have provided evidence for a secondary attractive interaction between the π-system of an aromatic substituent of the catalyst and the cationic allyl moiety, that in cooperation with stabilization of the developing negative charge on the oxyallyl fragment by hydrogen-bonding contributes to the preferred geometry of the transition state (Figure 40.4).

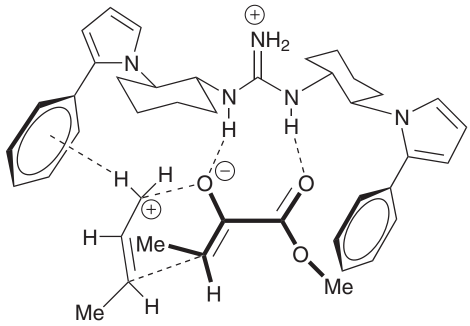
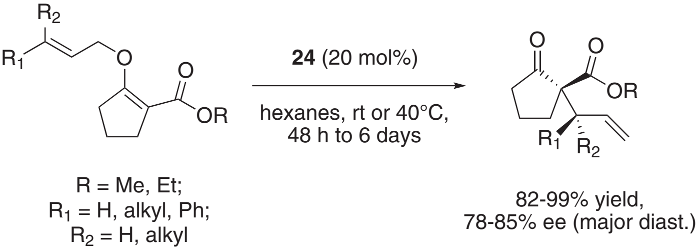


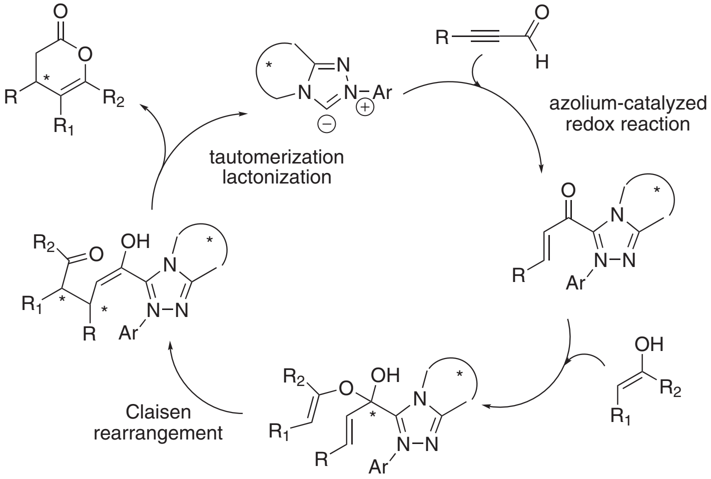
Figure 40.4 Transition state model for the guanidinium-catalyzed Claisen rearrangement.

This mechanistic analysis suggested that enhancement of the electron density at the phenyl substituents of the guanidinium ion would be beneficial for the reaction, and led to the development of a new *p*-(dimethylamino)phenyl-substituted catalyst **25**, which afforded better yields and stereoselectivities than the parent guanidinium **24** in a subset of substrates (Scheme 40.37) [45]. Catalyst **24** was also tested in the Claisen rearrangement of substituted *O*-allyl β-ketoesters, with excellent results (Scheme 40.38) [46]. Again, di- and tri-substituted compounds rearranged with high selectivity (from 5 : 1 dr to >20 : 1 dr) for the major diastereomer predicted by a six-membered chair-like transition state.



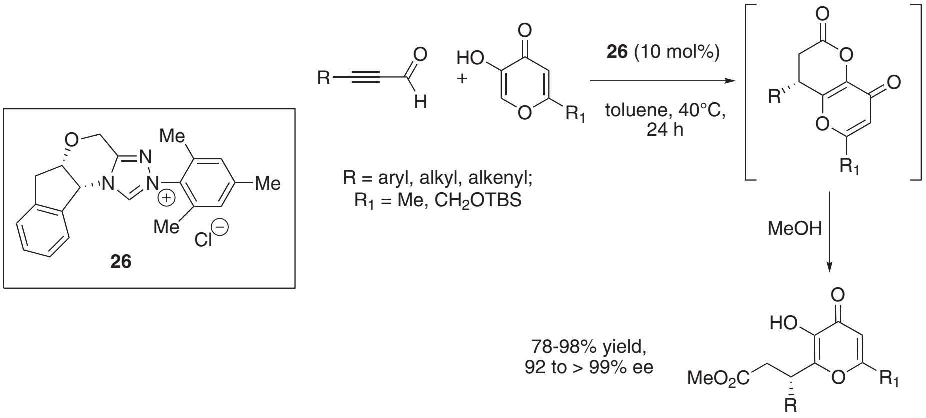
Scheme 40.38 Organocatalytic asymmetric rearrangement of substituted *O*-allyl β-ketoesters.

In 2010, Bode and coworkers published an enantioselective Claisen rearrangement catalyzed by chiral NHCs [47]. These authors studied the Coates modification of the Claisen rearrangement [48], which involves the rearrangement of an intermediate acetal obtained by thermal reaction between a stable enol and an acetal, and proposed a catalytic cycle consisting in an azolium-catalyzed redox reaction leading to an activated carboxylate [49], addition of the enol to this compound to give an intermediate that undergoes a Claisen rearrangement and affords a rearranged product that after tautomerization and lactonization gives a chiral lactone and regenerates the NHC catalyst (Scheme 40.39).



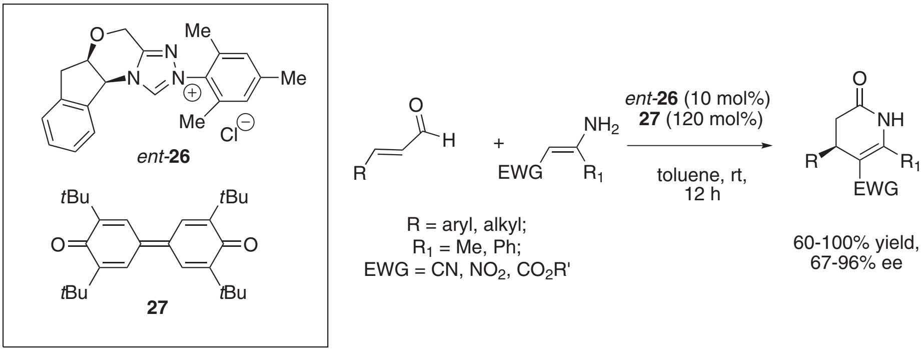
Scheme 40.39 Bode's proposal for a NHC-catalyzed Claisen rearrangement.

In the actual implementation of this concept, Bode and coworkers used 3-hydroxy-2-pyranone derivatives (kojic acids) as the enol components, and the lactone product was submitted *in situ* to ring-opening with methanol to afford the more stable methyl esters. Both the yields and the enantioselectivities were excellent, using the chiral triazolium salt **26** as the pre-catalyst (Scheme 40.40).



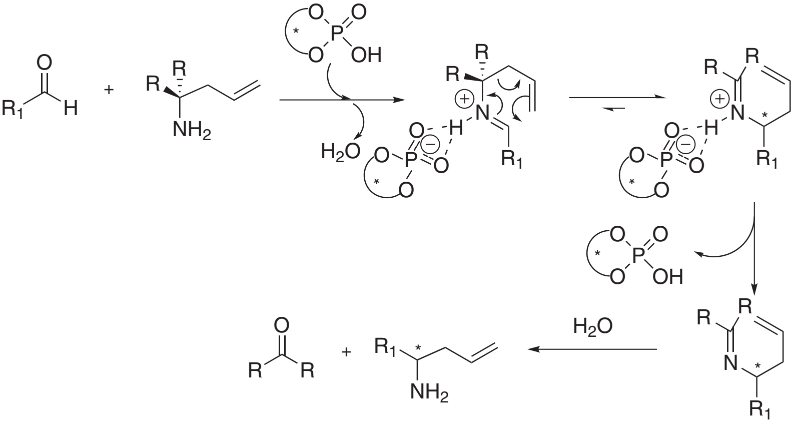
Scheme 40.40 Organocatalytic Coates–Claisen rearrangement with propargyl aldehydes and kojic acids.

Bode's research group subsequently reported a closely related process, in which an α,β-unsaturated aldehyde and a vinylogous amide react under catalysis by the NHC derived from *ent*-**26** and in the presence of stoichiometric amounts of an oxidant (Kharasch's quinone **27**) to give γ-substituted dihydropyridinones in good yields and enantioselectivities (Scheme 40.41) [50]. The mechanism of this process is probably very similar to that depicted in Scheme 40.39, except that the intermediate acyl azonium cation is generated from oxidation of the Breslow intermediate, resulting from reaction of the starting enal from the NHC catalyst, by the quinone **27**.



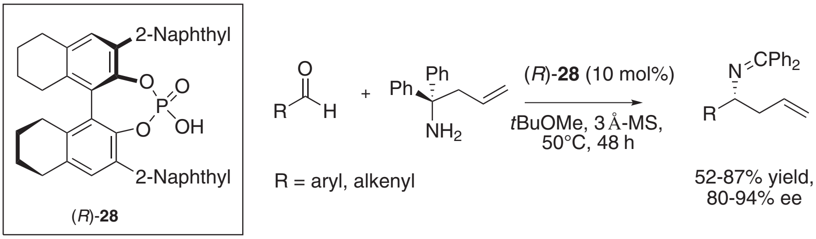
Scheme 40.41 NHC-catalyzed enantioselective annulation of enals and enamines via an aza-Claisen rearrangement.

Rueping and Antonchick [51] have examined the phosphoric acid diester-catalyzed 2-aza-Cope rearrangement [52], a transformation that provides an efficient entry to chiral homoallylic amines. They assumed that a phosphoric acid diester would both promote the *in situ* formation of an allyl iminium cation from an aldehyde and an achiral homoallylic amine, and the subsequent 2-azonia-Cope rearrangement. In a separate hydrolysis step, the rearranged homoallylic amine would furnish the target chiral amine (Scheme 40.42).



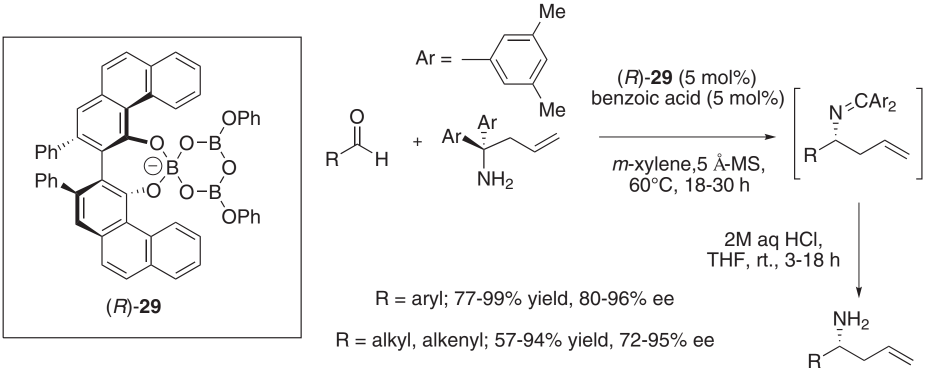
Scheme 40.42 Rueping's mechanistic proposal for a phosphoric acid diester-catalyzed 2-aza-Cope rearrangement.

After testing various binaphthol (BINOL) and octahydrobinaphthol phosphoric acid diesters, Rueping and Antonchick found that acid (*R*)-**28** was able to catalyze the asymmetric amination of cinnamaldehyde and of several aryl aldehydes in moderate to good yields and enantioselectivities (Scheme 40.43). The resulting homoallyl imines can be easily transformed into chiral primary (hydrolysis of the imine) or secondary (cyanoborohydride reduction of the imine) amines of absolute (*R*) configuration.



Scheme 40.43 Phosphoric acid diester-catalyzed enantioselective aminoallylation of aldehydes.

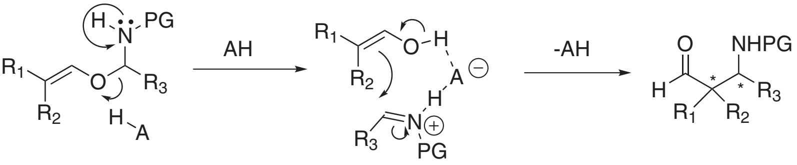
Later on, Ren and Wulff [53] reported that a combination of the chiral catalyst VANOL-B3 **29**, derived from the reaction of binaphthol derivative VANOL with triphenyl-borate, also afforded good results in the asymmetric catalytic aminoallylation of a series of aromatic, aliphatic, and α,β-unsaturated aldehydes. Catalytic amounts of benzoic acid were required to ensure the formation of the intermediate imines, and the rearranged imines were hydrolyzed *in situ* to afford the homoallylic amines (Scheme 40.44).



Scheme 40.44 Chiral borate-catalyzed enantioselective aminoallylation of aldehydes.

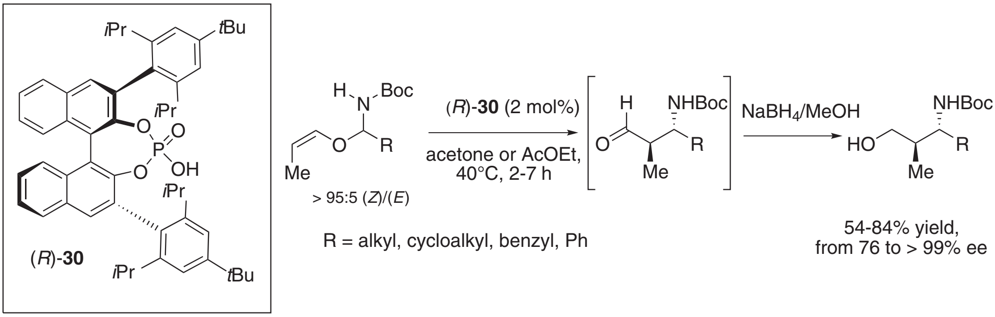
40.7
Aza-Petasis–Ferrier Rearrangement

The aza-Petasis–Ferrier rearrangement is not a true concerted sigmatropic reaction, since it is thought to proceed via C–O bond cleavage of a hemiaminal vinyl ether by the action of an acid catalyst to afford a reactive iminium cation and the enol form of an aldehyde; these two intermediates combine subsequently in a Mannich-type process, leading to β-amino aldehydes (Scheme 40.45) [54]. Recently, Terada and Toda used a BINOL-derived phosphoric acid diester as a catalyst for this interesting reaction [55].



Scheme 40.45 Acid-catalyzed aza-Petasis–Ferrier rearrangement.

The requisite hemiaminal vinyl ethers were stereoselectively obtained by a Ni(II)-catalyzed double-bond isomerization of the readily available hemiaminal allyl ethers. The authors found that the rearrangement could be efficiently catalyzed by means of the BINOL-derived phosphoric acid diester (*R*)-**30** (Scheme 40.46). Owing to the unstability of the resulting aldehydes, they were subsequently reduced to the corresponding γ-amino alcohols.



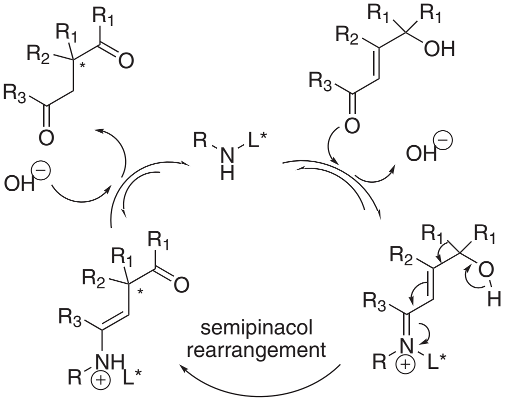
Scheme 40.46 Organocatalytic asymmetric aza-Petasis–Ferrier rearrangement.

The rearrangement was very stereospecific, with the (*Z*)-vinyl ethers leading to the almost exclusive (>95 : 5 dr) formation of the *anti*-diastereomers. The minor

(*E*)-isomers afforded the *syn*-diastereomers, also with good enantioselectivity. This asymmetric aza-Petasis–Ferrier rearrangement is thus complementary to the proline-catalyzed Mannich reactions with imines, which give rise to highly enantioenriched *syn*-β-amino aldehydes [4, 56].

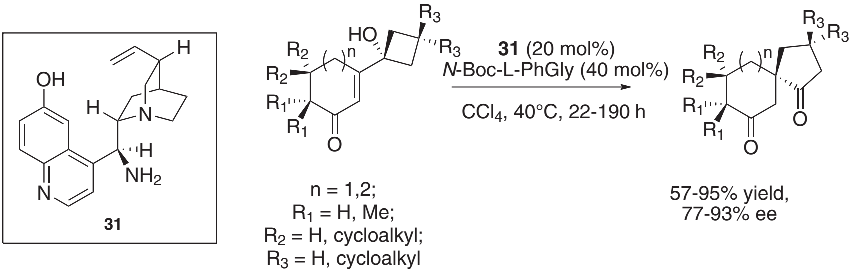
40.8
Pinacol and Related Rearrangements

The first enantioselective organocatalytic semipinacol rearrangement, by means of iminium catalysis, was disclosed by Tu and coworkers [57] in 2009. These authors envisaged that a chiral primary or secondary amine would trigger an asymmetric 1,2-carbon migration in suitably substituted α-ketols, according to the catalytic cycle outlined in Scheme 40.47.

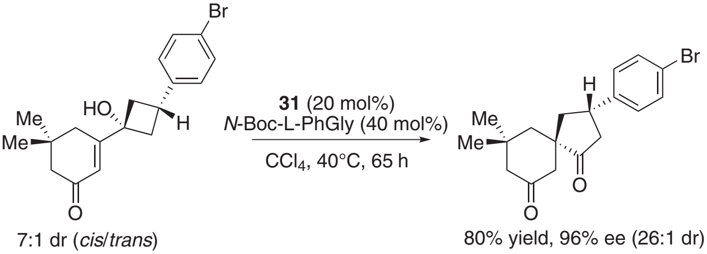


Scheme 40.47 Iminium catalysis in the vinylogous α-ketol rearrangement.

Tu and coworkers found that a combination of the cinchona-based primary amine **31** and *N*-Boc-L-phenylglycine was able to catalyze the semipinacol rearrangement of several cyclic enones bearing a substituted cyclobutanol moiety into spirocyclic diketones, in moderate to excellent yields and with good enantioselectivities (Scheme 40.48). Furthermore, Tu *et al.* showed that when the cyclobutanol moiety of the starting ketol was monosubstituted at C3 the rearrangement led to the formation of two stereocenters with excellent diastereo- and enantioselectivity, provided that the C3-substituent had a cis-relationship with respect to the tertiary hydroxyl, as exemplified in Scheme 40.49. The absolute configuration of the resulting spirocyclic diketone in this last example was ascertained by X ray crystallographic analysis.

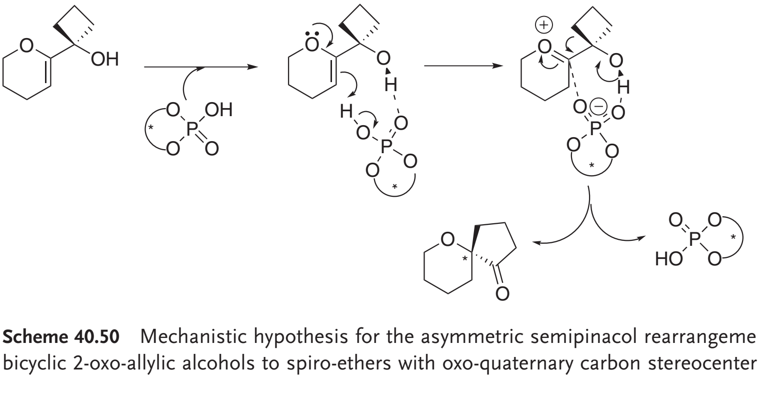


Scheme 40.48 Enantioselective vinylogous α-ketol rearrangement by iminium catalysis.



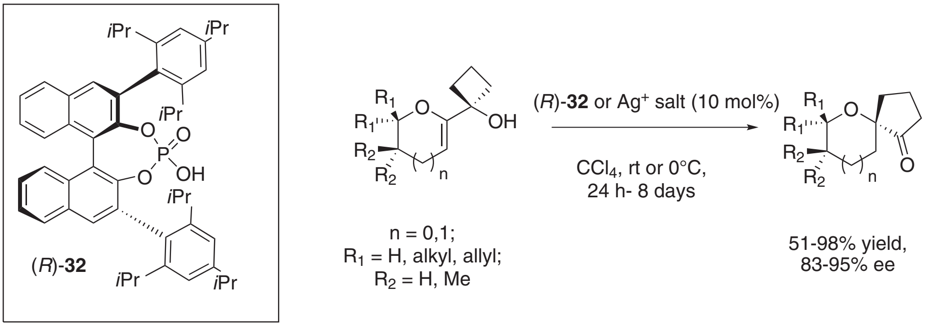
Scheme 40.49 Enantio- and diastereoselective semipinacol rearrangement of a 3-substituted cyclobutyl ketol.

Subsequently, the same research group reported a related, phosphoric acid diester-catalyzed semipinacol rearrangement for the asymmetric synthesis of chiral spiroethers [58]. They hypothesized that a BINOL-derived phosphoric acid diester could catalyze the semipinacol rearrangement of 2-oxo-allylic alcohols. In addition, they postulated that the asymmetric 1,2-migration might be triggered by *C*-protonation of the enol ether, facilitated by hydrogen bonding of the hydroxyl group of the substrate to the P=O oxygen of the phosphoric acid diester (Scheme 40.50).



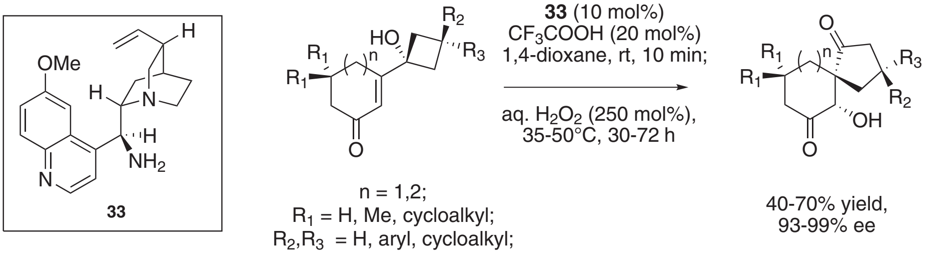
Scheme 40.50 Mechanistic hypothesis for the asymmetric semipinacol rearrangement of bicyclic 2-oxo-allylic alcohols to spiro-ethers with oxo-quaternary carbon stereocenters.

After screening several candidates, Tu and coworkers found that best results (up to 98% ee) were obtained with either the BINOL-derived phosphoric acid diester (*R*)-**32** (Scheme 40.51) or its silver salt.



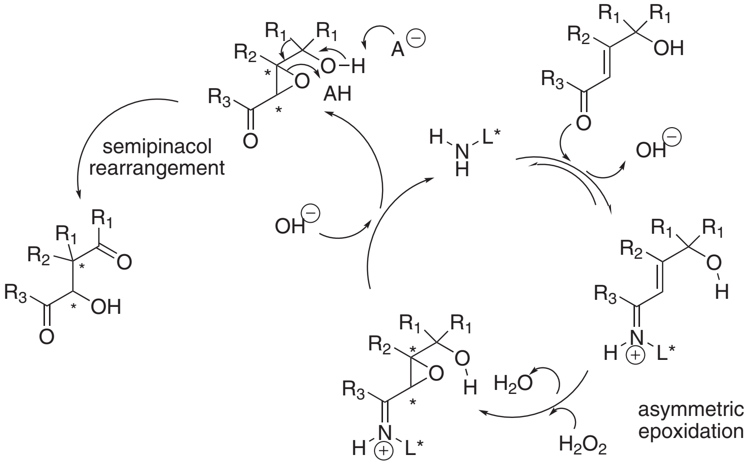
Scheme 40.51 Phosphoric acid diester-catalyzed enantioselective semipinacol rearrangement of 2-oxo-allylic alcohols.

More recently, Tu, Cao, and coworkers revealed that 9-deoxy-9-*epi*-aminoquinine **33** can catalyze both the asymmetric nucleophilic epoxidation of β-(1-hydroxycyclobutyl)enones and the subsequent semipinacol rearrangement of the resulting epoxide, to afford hydroxy-spirocycloalkane-diones with moderate to good yields and outstanding stereoselectivities (Scheme 40.52) [59].



Scheme 40.52 Organocatalytic asymmetric epoxidation/semipinacol rearrangement.

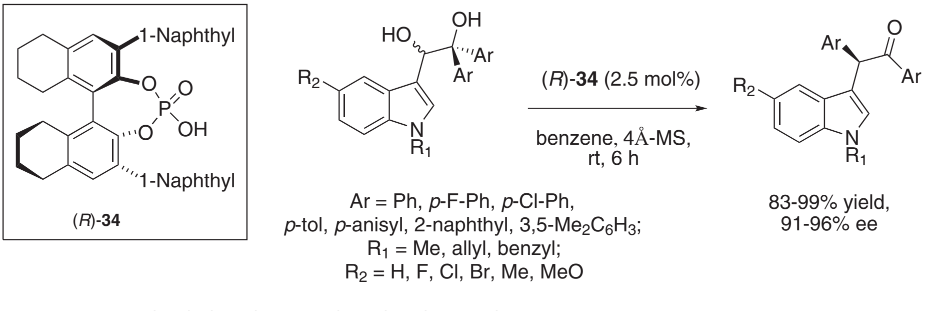
The proposed mechanism for this transformation is closely related to that depicted in Scheme 40.47 above, except that the intermediate iminium ion derived from the primary amine catalyst **32** is epoxidated stereoselectively [60] and, after hydrolysis of the iminium, an acid-induced diastereoselective semipinacol rearrangement affords the spirocyclic hydroxy-diketone product (Scheme 40.53).



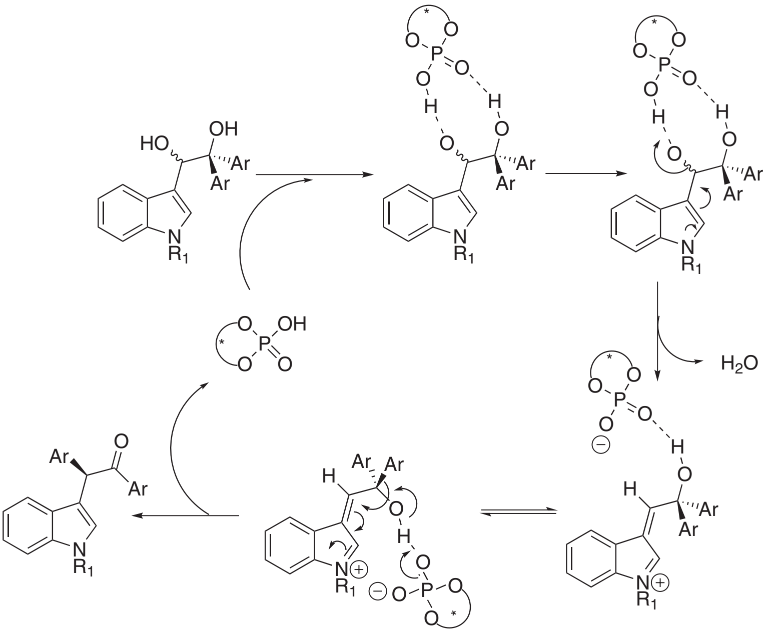
Scheme 40.53 Organocatalytic asymmetric Sepoxidation/semipinacol rearrangement.

Subsequently, organocatalytic asymmetric halogenation/semipinacol rearrangement sequences, both leading to chiral quaternary haloketones, have been reported by Tu and coworkers [61] and by Hennecke and coworkers [62]. The mechanism of these reactions probably involves an acid-catalyzed diastereoselective semipinacol rearrangement of a chiral halonium ion intermediate obtained by chiral tertiary amine-promoted asymmetric halogenation of an enone [63].

Antilla and coworkers [64] reported in 2010 the first Brønsted acid-catalyzed true pinacol rearrangement, in which the chiral phosphoric acid diester **34** was the best catalyst for the rearrangement of a series of indolyl diols (Scheme 40.54). A plausible mechanistic pathway for this transformation begins with the acid-induced dehydration of the starting indolyl diol to an intermediate iminium ion, followed by a 1,2-aryl shift (Scheme 40.55).



Scheme 40.54 Chiral phosphoric acid-catalyzed pinacol rearrangement.



Scheme 40.55 Proposed mechanistic pathway for the chiral phosphoric acid-catalyzed pinacol rearrangement.

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41
Regio- and Position Selective Reactions and Desymmetrizations

Alan C. Spivey and Stellios Arseniyadis

41.1
Introduction

The use of enantiomerically enriched small molecule chiral nucleophiles as organocatalysts for the asymmetric preparation of various important classes of chiral fine chemicals has been intensively investigated over the last two decades [1–3]. Initial focus centered largely on the acylative kinetic resolution (KR) and asymmetric desymmetrization (ASD) of racemic secondary alcohols and *meso*-diols, respectively, to give the corresponding esters using substoichiometric amounts of various nucleophilic chiral amines and phosphines in conjunction with stoichiometric quantities of appropriate acyl donors [4–8]. Increasingly, however, and reflecting the rapid maturation of this field, attention is broadening to encompass mechanistically related processes for the asymmetric phosphorylation, phosphitylation, sulfonylation, sulfinylation, and silylation of alcohols and for the asymmetric acylation of amines and of carbon nucleophiles [9, 10]. Since the historical development of the field as well as many of the more recent advances have been comprehensively reviewed, the following is designed to provide an update on recent developments with a particular emphasis on current challenges and trends in nucleophile-catalyzed asymmetric group transfer to oxygen and nitrogen atoms; related transformations involving acyl and carboxyl transfer to carbon (e.g., [1,3]-Steglich-type rearrangements) [11] have not been included.

41.2
Kinetic Resolution of Alcohols

41.2.1
Acylation-Based Processes

Chiral secondary alcohols represent an important class of compounds prevalent in several biologically active natural products as well as in various pharmaceuticals and agrochemicals. They are also particularly useful synthetic intermediates,

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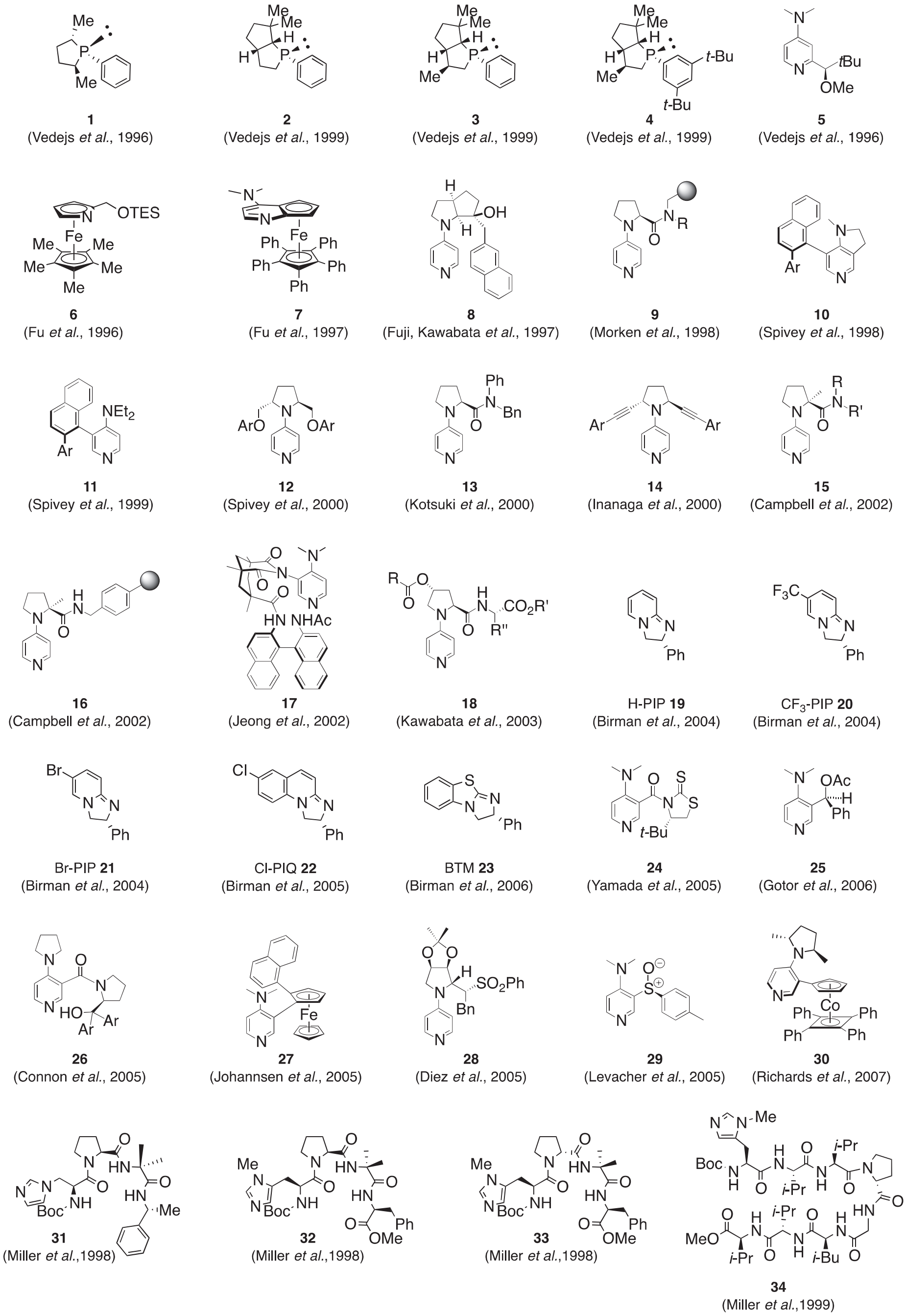
finding employment in virtually all areas of organic chemistry. As a consequence, several useful synthetic methods have been specifically designed to access this particular motif in a highly enantioselective fashion [12]. Nonetheless, chiral secondary alcohols can also be obtained through KR of racemates [13]. This transformation has traditionally been carried out using enzymes [14], particularly lipases and esterases, which can provide high levels of selectivity (*s*, selectivity factor) for a wide variety of racemic alcohols. Unfortunately, the preparative use of enzymes is often associated with several limitations such as their high cost, the need for specific operating conditions, low batch-to-batch reproducibility, and, most importantly, their availability in only one enantiomeric form. Consequently, over the last two decades there have been significant efforts dedicated to the development of small molecule chiral catalysts capable of mediating the KR and ASD of alcohols by enantioselective acylation and related processes [8–10, 15], notably by Vedejs [16, 17], Fu [18], Fuji and Kawabata [19], Morken [20], Spivey [21], Miller [22], Kotsuki [23], Inanaga [24], Campbell [25], Jeong [26], Birman [27], Ishihara [28], Yamada [29], Gotor [30], Connon [31], Johannsen [32], Diez [33], Levacher [34], and Richards [35] (Figure 41.1).

41.2.1.1 **Mechanistic Studies**

As mentioned above, since the pioneering work of Wegler *et al*. [36] in the field of alcohol KR through asymmetric acylation, tremendous efforts have been dedicated to designing efficient catalytic systems.

Not only have great strides been made in terms of synthetic studies directed at uncovering ever more selective and useful nucleophilic catalysts but, in parallel, significant advances have been made towards understanding the fundamental mechanistic nuances and stereochemical subtleties of these reactions using physical organic experimentation and theoretical modeling. Of particular note has been the large body of work emanating from the groups of Mayr and Zipse in Munich directed at illuminating and quantifying the carbon nucleophilicities of a range of *tert*-amines, pyridines, and phosphanes by reference to their interactions with benzhydrilium cations (Ar_2CH^+) [37–40], with methyl cations (methyl cation affinity, MCA) [41], and with so-called “Mosher’s cations” ($PhOMeCF_3^+$) [42]. One aim of these studies has been to explore how the carbon nucleophilicities (i.e., rates of reactions with carbon-based electrophiles; a kinetic parameter) and carbon basicities (i.e., equilibrium constants for Lewis adduct formation with carbon-centered Lewis bases; a thermodynamic parameter) for these types of nucleophiles correlate with their reactivity and efficiency as nucleophilic organocatalysts and whether these parameters offer superior descriptors to the classical proton affinity (PA) and pK_a, respectively, for predicting such behavior. For example, 4-DMAP [4-(dimethylamino)pyridine] and various phosphanes were found to have comparable carbon nucleophilicities (towards benzhydryl cations) and also similar carbon basicities (towards benzhydryl cations) despite having widely differing Brønsted basicities [37]. Given that both 4-DMAP and phosphanes are often found to display broadly comparable catalytic rates, in for example, alcohol acylation and Baylis–Hillman reactions, it is clear that these parameters can provide a good measure of catalytic



1 (Vedejs *et al.*, 1996)
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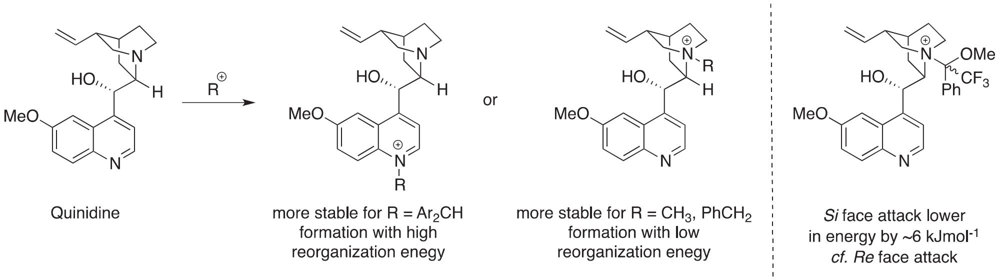
5 (Vedejs *et al.*, 1996)
6 (Fu *et al.*, 1996)
7 (Fu *et al.*, 1997)
8 (Fuji, Kawabata *et al.*, 1997)
9 (Morken *et al.*, 1998)
10 (Spivey *et al.*, 1998)
11 (Spivey *et al.*, 1999)
12 (Spivey *et al.*, 2000)
13 (Kotsuki *et al.*, 2000)
14 (Inanaga *et al.*, 2000)
15 (Campbell *et al.*, 2002)
16 (Campbell *et al.*, 2002)
17 (Jeong *et al.*, 2002)
18 (Kawabata *et al.*, 2003)
H-PIP **19** (Birman *et al.*, 2004)
CF_3-PIP **20** (Birman *et al.*, 2004)
Br-PIP **21** (Birman *et al.*, 2004)
Cl-PIQ **22** (Birman *et al.*, 2005)
BTM **23** (Birman *et al.*, 2006)
24 (Yamada *et al.*, 2005)
25 (Gotor *et al.*, 2006)
26 (Connon *et al.*, 2005)
27 (Johannsen *et al.*, 2005)
28 (Diez *et al.*, 2005)
29 (Levacher *et al.*, 2005)
30 (Richards *et al.*, 2007)
31 (Miller *et al.*,1998)
32 (Miller *et al.*,1998)
33 (Miller *et al.*,1998)
34 (Miller *et al.*,1999)

Figure 41.1 Example of catalysts for the KR of racemic alcohols. Boc = *tert*-butoxycarbonyl; BTM = benzotetramisole; PIP = 2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine; PIQ = 2-phenyl-1,2-dihydroimidazo[1,2-*a*]quinoline; TES = triethylsilyl.

potential. Of course, the combination of kinetic nucleophilicity and thermodynamic carbon basicity data allows the relative nucleofugalities of these species to be inferred – a factor that is of crucial importance in most catalytic cycles, including those proposed for many nucleophile-catalyzed group-transfer reactions of the type discussed in this chapter. The reasons for the superior predictive value of carbon nucleophilicity/carbon basicity data, as compared to proton affinity/pK_a data, in the context of many organonucleophile-mediated processes, particularly those involving phosphanes, appears to be a combination of more realistic steric terms and better accounting for differences in bond strengths between second and third row elements, for example, N–C and P–C bonds compared with N–H and P–H bonds [41].

Mayr and Zipse have used this type of analysis to particular effect to understand the relative efficiencies of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in Baylis–Hillman reactions [38], the reasons for the superior catalytic efficiencies of 3,4,5-triaminosubstitutedpyridine "super-DMAPs" relative to 4-DMAP itself [40], and, perhaps most intriguingly, the roles of the quinuclidine and quinoline nitrogens as nucleophilic centers when cinchona alkaloids such as quinine are employed as organocatalysts (Scheme 41.1) [39, 42].



Quinidine

more stable for R = Ar_2CH formation with high reorganization enegy

more stable for R = CH_3, $PhCH_2$ formation with low reorganization enegy

Si face attack lower in energy by ~6 $kJmol^{-1}$ *cf. Re* face attack

Scheme 41.1 The different nucleophilic characters of the quinuclidine and quinoline nitrogens in quinine as revealed by physical organic studies by Mayr and Zipse *et al.*

Using both computational and experimental techniques, initial studies demonstrated that the position of reaction with a given electrophile was dependent on its size [39]. Related studies, using the prochiral cation derived from decarboxylation of Mosher's acid as a probe, computationally estimated the difference in energy between the adducts formed from *Re* and *Si* face attack on this cation as an indicator of stereoinductive potential [42].

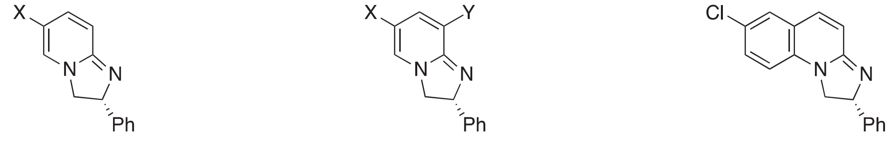
Related studies by Zipse *et al.* [43] have interrogated acylation events directly using experimental kinetic measurements and computation to assess steric effects in the uncatalyzed versus the 4-DMAP catalyzed acylation of various alcohols by anhydrides in order to quantify the "window of opportunity" in KR experiments [44]. The results obtained correlated well with prior experimental data in the literature in so far as it was found that, for secondary alcohols, the maximal difference in rate between the background reaction and the catalyzed reaction is expected when employing isobutyric anhydride (as is commonly employed in 4-DMAP catalyzed KR and ASD reactions). Moreover, the very low intrinsic reactivity of *tert*-alcohols, in combination with their small background versus catalyzed differential rate with all anhydrides investigated, rationalizes the severe challenge posed by KR of this substrate class.

A detailed structural analysis of a series of N-acetylated 4-DMAP salts using X-ray crystallography, variable-temperature IR and NMR spectroscopy as well as DFT (density functional theory) computation has been reported by Schreiner *et al.* [45] The N-acetyl (Ac) and N-trifluoroacetyl salts of 4-DMAP having chloride, acetate, and trifluoroacetate counterions were examined and the structural features correlated to known features of 4-DMAP-catalyzed acylation reactions. The counterions were found to occupy positions in which the angles between the nucleophilic center of the anion and the carbonyl carbon atom of the N-acetyl moiety map onto the Bürgi–Dunitz trajectory and the salts with relatively high ion-pair mobilities appeared to correlate with the catalytically most active species, as had been speculated previously [46]. Additionally, the role of H-bonding between the hydrogen at C2 of the 4-DMAP and the acetate-type counterions was noted. This type of interaction has also been suggested by Bourissou *et al.* to be crucial in explaining the high reactivity of 4-DMAP for the ring-opening polymerization of lactide and lactic *O*-carboxylic anhydride [47]. This group performed DFT calculations that indicated that in these catalytic processes involving ring-opening by methanol the role of 4-DMAP is as a Brønsted base at the pyridyl nitrogen and as an acid at the C2 hydrogen in a bifunctional activation step, unlike in secondary alcohol acylation by anhydrides [48].

A recently disclosed study by Burke *et al.* [49] with the potential for significant impact in directing the development of chiral 4-DMAP-type acylation catalysts correlates the rate of acylation of different alcohol groups within complex polyols with the electronic nature of the acylating agent employed. A Hammett analysis is proposed to be consistent with linking this phenomenon to the Hammond postulate: electronic tuning towards a more "product-like" transition state amplifies site-discriminating interactions between the active catalytic species and its substrate. This concept was used to transform a minimally site-selective alcohol acylation reaction of an amphotericin B derivative into a highly site-selective one of preparative utility.

41.2.1.2 **Synthetic Studies**

In 2004, Birman *et al.* began their quest to develop an easily accessible and highly effective acylation catalyst for the KR of secondary alcohols. The first chiral derivative to be prepared and tested was based on the 2,3-dihydroimidazo[1,2-*a*]-pyridine (DHIP) core, itself derived from (*R*)-2-phenylglycinol (Figure 41.2). (*R*)-2-Phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine (**35**, H-PIP) [27a] afforded the KR of (±)-phenylethylcarbinol in a promising 49% ee (enantiomeric excess) albeit with a low conversion (21% conversion, $s = 3.3$). To increase the electrophilicity of the acylated intermediate and thus improve the reactivity of the catalyst, an electron-withdrawing

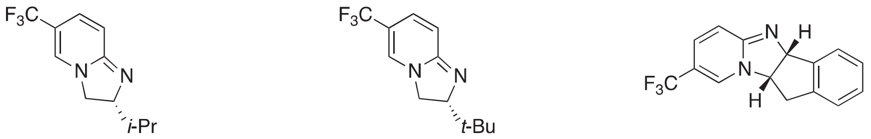


X-PIP (2004)
20 (X = CF_3), **21** (X = Br)
35 (X = H), **36** (X = NO_2)

X-PIP analogs (2006)
37 (X = $CONEt_2$, Y = H), **38** (X = CN, Y = H)
39 (X = H, Y = F), **40** (X = Br, Y = Br)

Cl-PIQ **22** (2005)

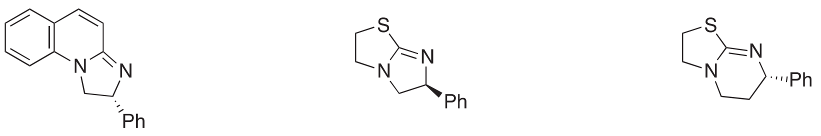
Figure 41.2 Structure of various 2-phenyldihydroimidazo[1,2-*a*]pyridine catalysts.



CF_3-PIP analogue **41** (2006)

CF_3-PIP analogue **42** (2006)

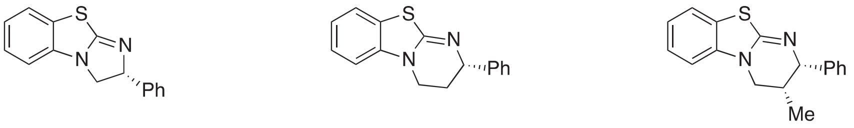
CF_3-PIP analogue **43** (2006)



DHIQ **44** (2006)

Tetramisole **45** (2006)

Homotetramisole **46** (2008)



BTM **23** (2006)

HBTM **47** (2008)

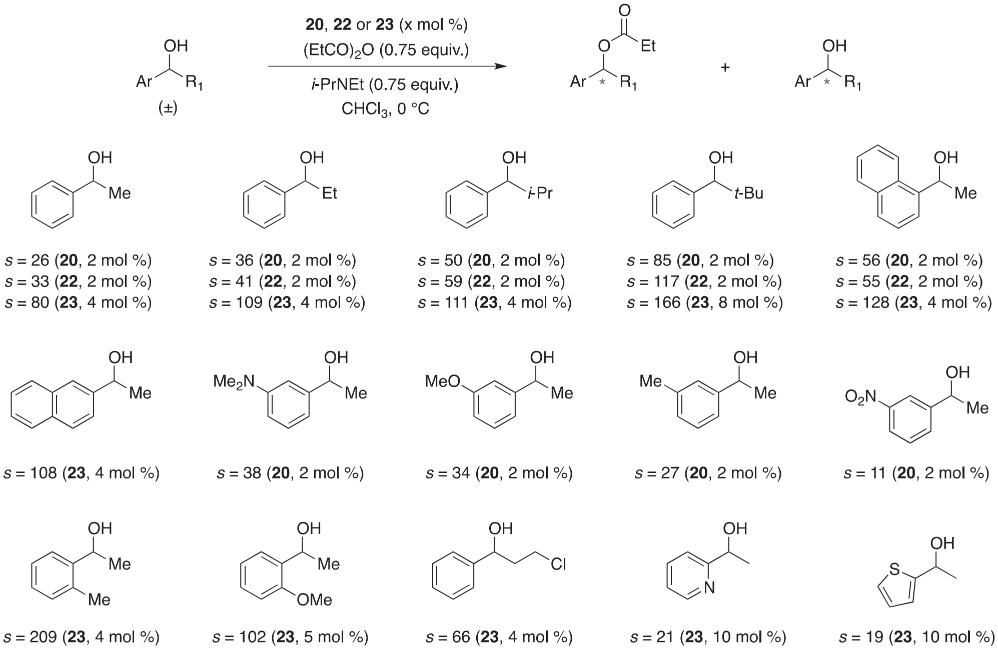
Me-HBTM **48** (2009)

Figure 41.3 Structure of amidine-based catalysts developed by Birman *et al.*

substituent was introduced on the pyridine ring. Hence, three new derivatives [CF_3-PIP (**20**), Br-PIP (**21**), and NO_2-PIP (**36**), Figure 41.2] where synthesized and tested under otherwise identical conditions. Interestingly, two DHIP (dihydroimidazo[1,2-*a*]pyridine) derivatives, CF_3-PIP (**20**) and Cl-PIQ (**22**), proved to be particularly effective when combined with $(EtCO)_2O$ and *i*-Pr_2NEt in promoting the KR of benzylic and allylic alcohols with good to excellent selectivities ($s = 26$–85). Comparatively, the additional π–π interaction brought about by replacement of the pyridine ring with a quinoline led to a significant improvement in the catalytic efficacy [27a, 27b].

Subsequently, Birman *et al.* tested various amidine-based catalysts, including commercially available tetramisole (**45**) and its benzannellated analog benzotetramisole (BTM) (**23**) in the KR of secondary aryl alkyl alcohols and propargylic alcohols (Figure 41.3). Both catalysts displayed far superior enantioselectivity although BTM proved to be more reactive [27c, 50, 51].

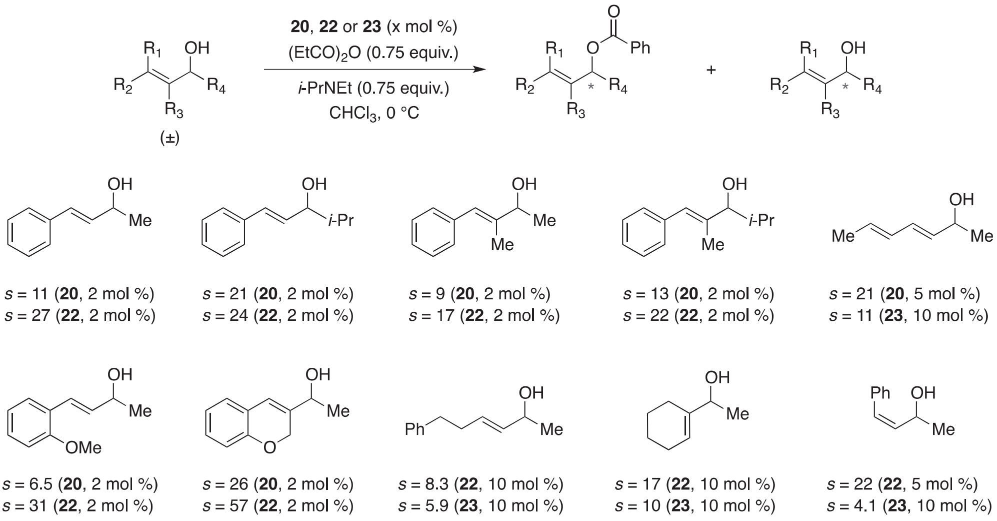
All three imidazoline-based catalysts CF_3-PIP (**20**), Cl-PIQ (**22**), and BTM (**23**) displayed high selectivities in the KR of benzylic alcohols, ranging from $s = 11$ to $s = 209$ (Scheme 41.2) [52]. As a general trend, electron-rich *meta*-substituted compounds were resolved with higher selectivities than ones bearing an electron-withdrawing group at the same position, while secondary aryl alkyl alcohols bearing a substituent at the *ortho* position of the aromatic ring were resolved with the highest levels of selectivity.



Scheme 41.2 Kinetic resolution of secondary aryl alkyl alcohols by Birman *et al.*

Initial attempts to achieve the KR of allylic alcohols using CF_3-PIP (**20**) resulted in only moderate selectivities, which could be improved by extending the π-system of the catalyst. Indeed, the use of the second-generation catalyst, Cl-PIQ (**22**), not only afforded higher reaction rates but also higher levels of selectivity (up to $s = 57$) in the KR of all the cinnamyl alcohols examined independently of the substitution pattern on the aromatic ring (Scheme 41.3). Interestingly, the third-generation catalyst BTM (**23**), which induced higher selectivities in the case of secondary aryl alkyl alcohols, turned out to be less suitable for the KR of allylic alcohols, affording lower selectivities and requiring extended reaction time and additional catalyst loading.

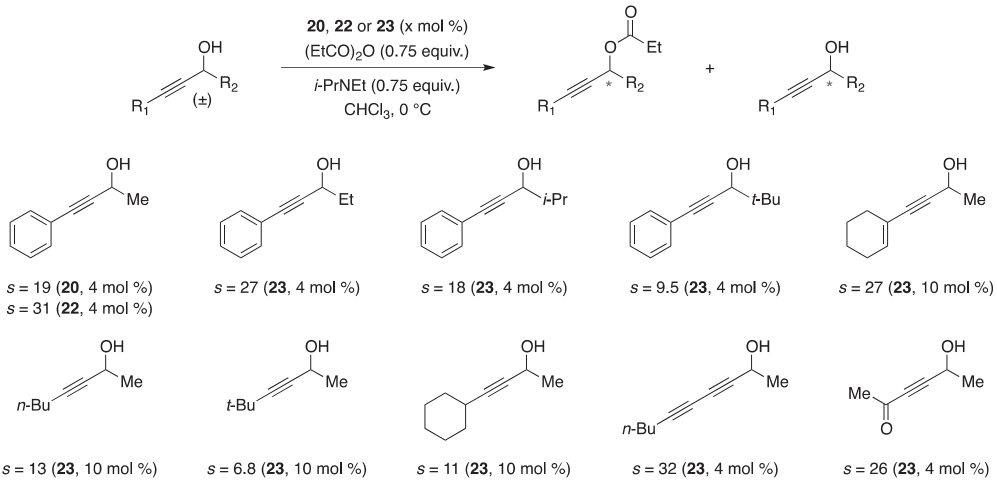
Propargylic alcohols could also be resolved using amidine-based catalysts such as CF_3-PIP (**20**), Cl-PIQ (**22**), and BTM (**23**) [50]. However, the latter proved to be much more efficient, affording selectivity factors ranging from $s = 6.8$ to 32



Scheme 41.3 Kinetic resolution of allylic alcohols by Birman *et al.*

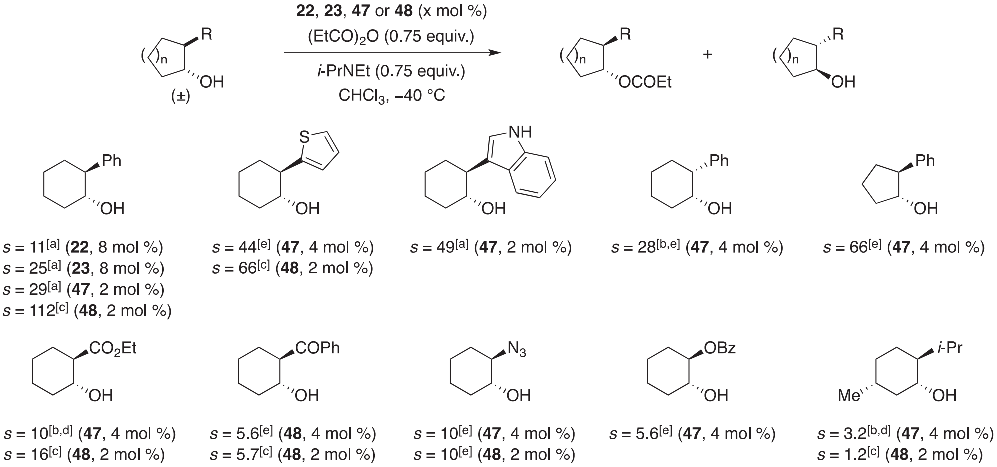
(Scheme 41.4). In contrast with the results obtained with secondary aryl alkyl alcohols, increasing the size of the alkyl group α to the hydroxyl led to lower selectivities. In addition, propargylic alcohols bearing an aryl, an alkenyl, an alkynyl, or an acyl group on the alkyne moiety were resolved with higher selectivities (up to $s = 32$) than those bearing an aliphatic side chain (up to $s = 11$).

Cl-PIQ (**22**) and BTM (**23**) also proved to be effective catalysts for the KR of substituted cycloalkanols even though the reactions were rather sluggish and



Scheme 41.4 Kinetic resolution of propargylic alcohols by Birman *et al.*

required higher catalyst loadings (Scheme 41.5) [51]. Interestingly, under the same reaction conditions, homobenzotetramisole (HBTM, **47**) and its analog Me-HBTM (**48**) proved to be generally more reactive and induced higher selectivities, affording the KR of racemic cycloalkanols with selectivity factors up to *s* = 112. Once again, π-interactions appeared to be critical for chiral recognition.



$s = 11^{[a]}$ (**22**, 8 mol %)
$s = 25^{[a]}$ (**23**, 8 mol %)
$s = 29^{[a]}$ (**47**, 2 mol %)
$s = 112^{[c]}$ (**48**, 2 mol %)

$s = 44^{[e]}$ (**47**, 4 mol %)
$s = 66^{[c]}$ (**48**, 2 mol %)

$s = 49^{[a]}$ (**47**, 2 mol %)

$s = 28^{[b,e]}$ (**47**, 4 mol %)

$s = 66^{[e]}$ (**47**, 4 mol %)

$s = 10^{[b,d]}$ (**47**, 4 mol %)
$s = 16^{[c]}$ (**48**, 2 mol %)

$s = 5.6^{[e]}$ (**48**, 4 mol %)
$s = 5.7^{[c]}$ (**48**, 2 mol %)

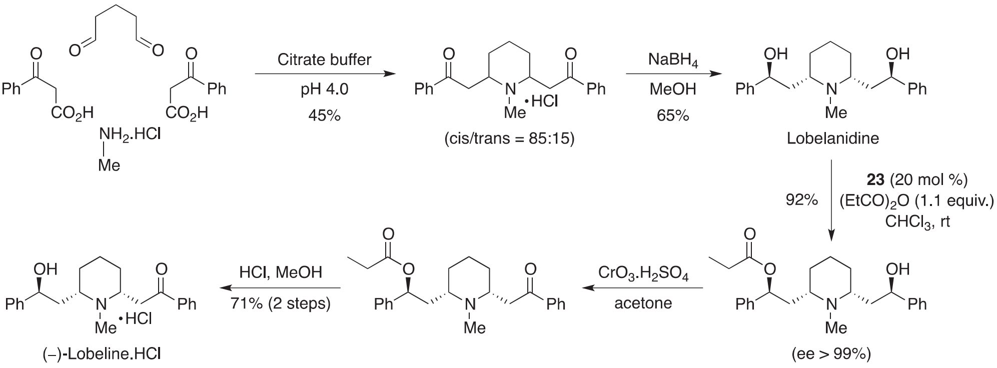
$s = 10^{[e]}$ (**47**, 4 mol %)
$s = 10^{[e]}$ (**48**, 2 mol %)

$s = 5.6^{[e]}$ (**47**, 4 mol %)

$s = 3.2^{[b,d]}$ (**47**, 4 mol %)
$s = 1.2^{[c]}$ (**48**, 2 mol %)

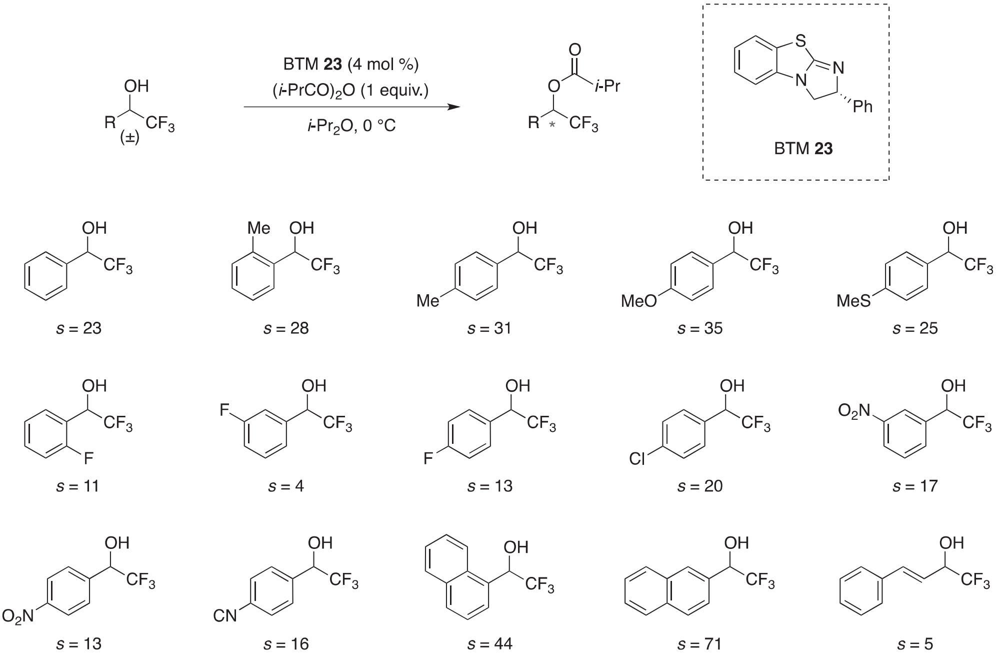
Scheme 41.5 Kinetic resolution of cycloalkanols by Birman *et al*. The reaction was carried out [a] at 23 °C; [b] at −10 °C; [c] in toluene; [d] in *tert*-amyl alcohol; [e] in a toluene/*tert*-amyl alcohol mixture.

In 2007, Birman *et al*. showed that BTM (**23**) could also be used as a powerful desymmetrization agent [53]. Indeed, by subjecting lobelanidine to 20 mol% of **23** in the presence of propionic acid anhydride (1.1 equiv.) in $CHCl_3$ at room temperature, the corresponding propionic ester was obtained in quasi-enantiopure form and up to 92% yield. Jones oxidation and subsequent hydrolysis eventually resulted in the isolation of (−)-lobeline, a natural product exhibiting anti-asthmatic, expectorant, and respiratory stimulant activities (Scheme 41.6).



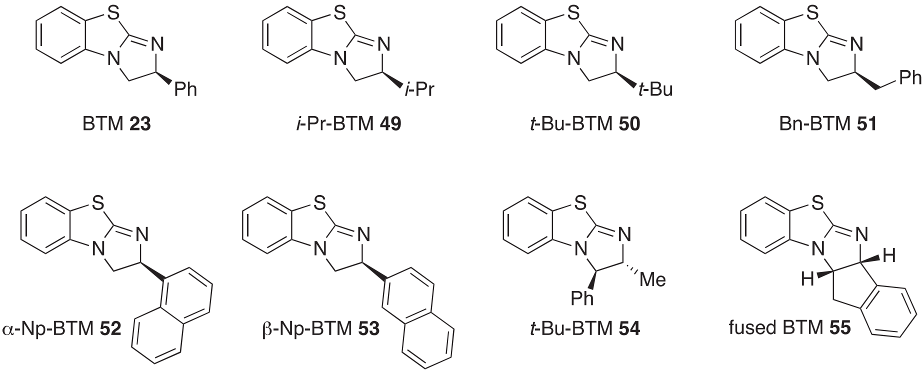
Scheme 41.6 Synthesis of (−)-lobeline by Birman *et al*.

Later, Chen and coworkers demonstrated that (*R*)-BTM (**23**) could be successfully used in the KR of a series of 2,2,2-trifluoro-1-aryl ethanol, affording *s* values up to 47 at room temperature (Scheme 41.7) [54]. Additionally, they were able to show that the method was amenable to preparative scale, affording both the acylated product and the unreacted alcohol with high ees and reasonable yields.



Scheme 41.7 BTM-catalyzed KR of racemic 2,2,2-trifluoro-1-aryl-ethanol by Chen *et al.*

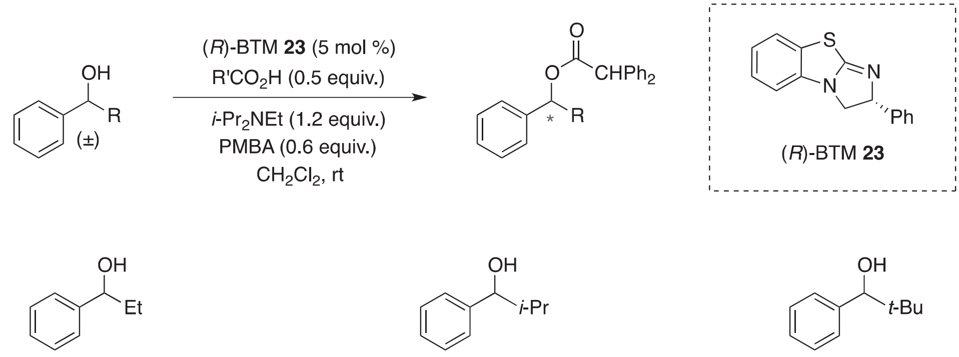
In 2007 Shiina *et al.* screened various tetramisole-based catalysts (Figure 41.4) to develop the first example of an alcohol KR process using free carboxylic acids as acylating agents [55]. In their protocol, unreactive anhydrides such as *para*-methoxybenzoic anhydride (PMBA) or pivalic anhydride were used to activate the catalyst by *in situ* formation of the corresponding chiral mixed anhydride. The best selectivities were obtained using 5 mol% of BTM (**23**) in conjunction with PMBA, affording the KR of a series of secondary aryl alkyl alcohols with selectivity factors as high as $s = 88$ at room temperature (Scheme 41.8).



BTM **23** *i*-Pr-BTM **49** *t*-Bu-BTM **50** Bn-BTM **51**

α-Np-BTM **52** β-Np-BTM **53** *t*-Bu-BTM **54** fused BTM **55**

Figure 41.4 Structure of various tetramisole-based catalysts.



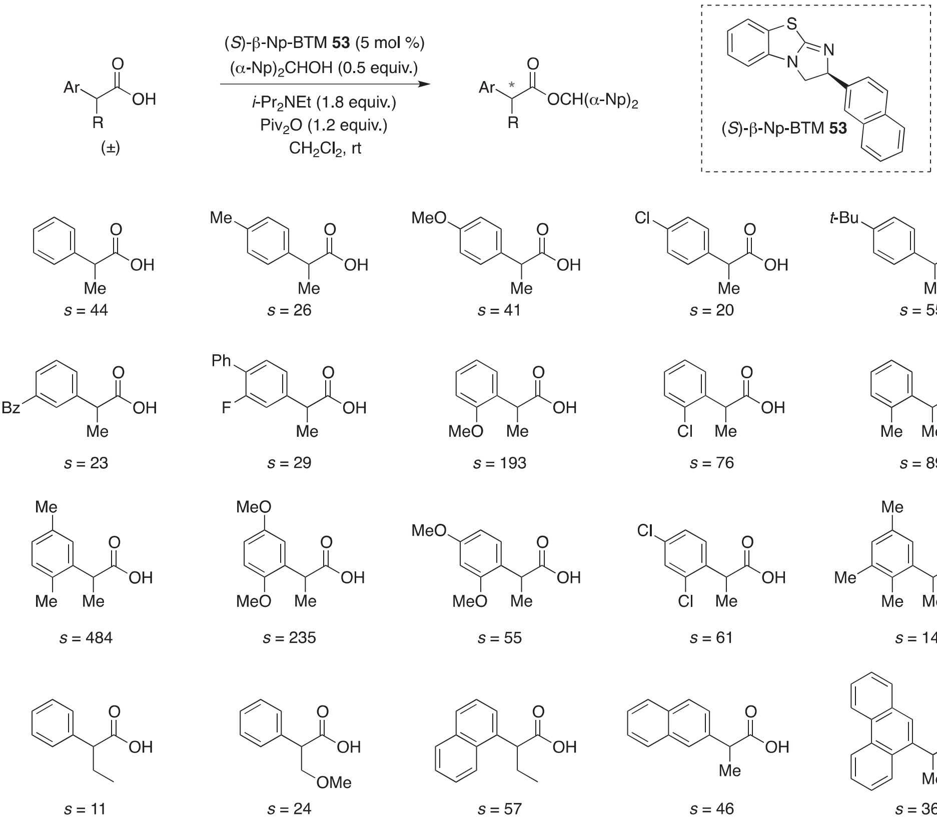
s = 39 (R = Et)
s = 43 (R = $(CH_2)_2Ph$)
s = 39 (R = $(CH_2)_3Ph$)
s = 23 (R = $(CH_2)_2CHMe_2$)
s = 42 (R = $(CH_2)_2CH{=}CH_2$)
s = 15 (R = CH_2OMe)

s = 47 (R = Et)
s = 46 (R = $(CH_2)_2Ph$)

s = 42 (R = Et)
s = 88 (R = $(CH_2)_2Ph$)

Scheme 41.8 Kinetic resolution of secondary aryl alkyl alcohols by Shiina *et al.*

Subsequently, Shiina *et al.* developed a practical method for the KR of racemic carboxylic acids involving an achiral alcohol, PMBA or pivalic anhydride, and a tetramisole-based catalyst [56]. After an exhaustive parameter screen, it was shown that a combination of bis(α-naphthyl)methanol, pivalic anhydride, and (*S*)-β-Np-BTM (**53**) induced the best levels of selectivity at room temperature, affording the corresponding esters with high *s* factors ranging from *s* = 20 to 484 (Scheme 41.9).

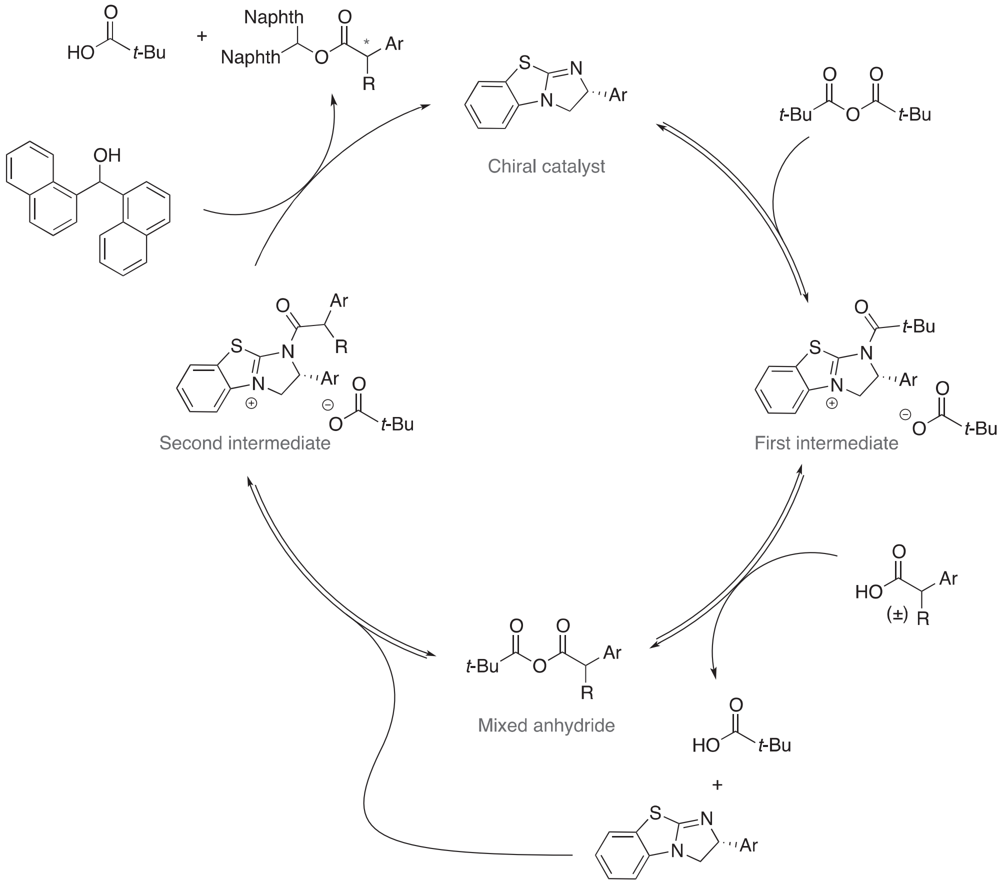


Scheme 41.9 Kinetic resolution of racemic carboxylic acids by Shiina *et al.* (Naphth = naphthyl).

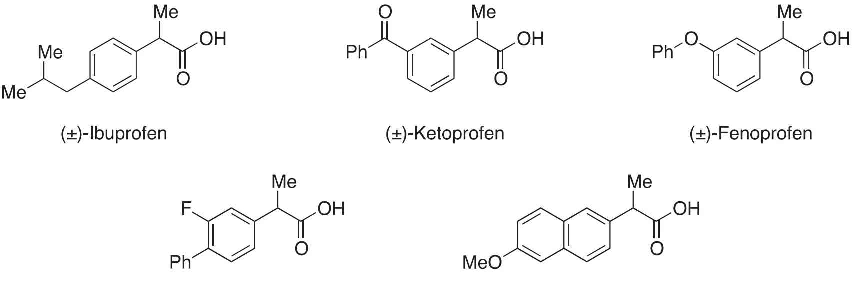
The reaction proceeds via the formation of a first chiral zwitterionic intermediate from pivalic anhydride and the amidine-based catalyst. A mixed anhydride is then generated in the presence of the racemic carboxylic acid and activated by the chiral acyl-transfer catalyst to form the second zwitterionic intermediate. The latter species selectively reacts with a nucleophilic alcohol to afford the desired enantioenriched carboxylic ester (Scheme 41.10).

After fine-tuning the nucleophile and the BTM catalyst, this method was eventually used in the KR of ibuprofen (*s* = 34), ketoprofen (*s* = 14), fenoprofen (*s* = 17), flurbiprofen (*s* = 15), and naproxen (*s* = 61), five chiral non-steroidal anti-inflammatory drugs (Figure 41.5).

In 2010, a similar strategy was successfully applied to the KR of various 2-hydroxy alkanoates [57]. Indeed, the combination of BTM (**23**), pivalic anhydride, and diphenylacetic acid effectively produced the corresponding 2-acyloxyalkanoates in selectivities ranging from *s* = 47 to 202 (Scheme 41.11).



Scheme 41.10 Proposed mechanism for the tetramisole-catalyzed KR of racemic carboxylic acids.



(±)-Ibuprofen

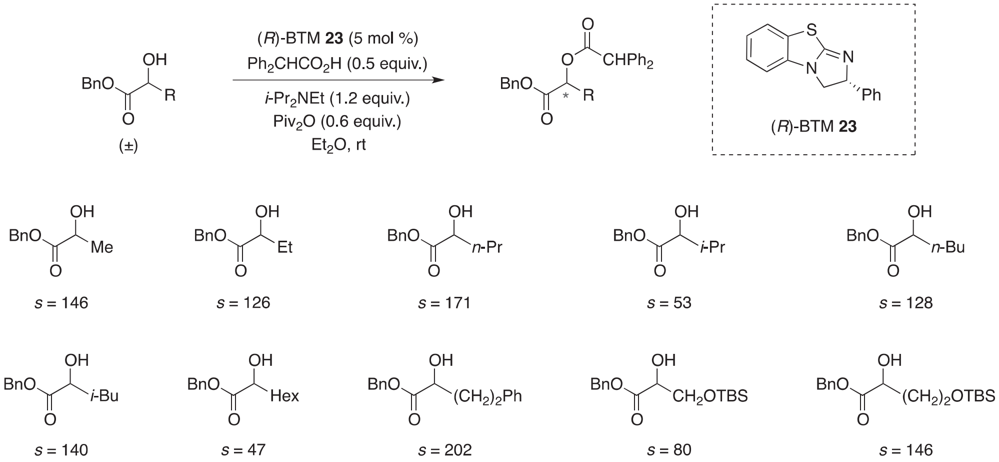
(±)-Ketoprofen

(±)-Fenoprofen

(±)-Flurbiprofen

(±)-Naproxen

Figure 41.5 Structures of ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and naproxen.

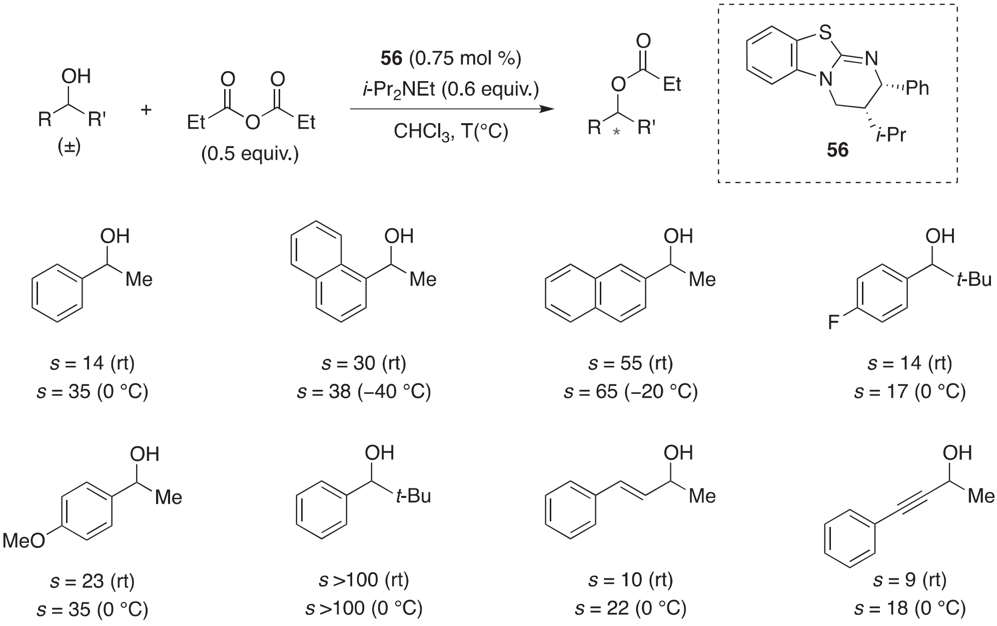


Scheme 41.11 Kinetic resolution of racemic 2-hydroxyalkanoates by Shiina *et al.* (TBS = tributyldimethylsilyl).

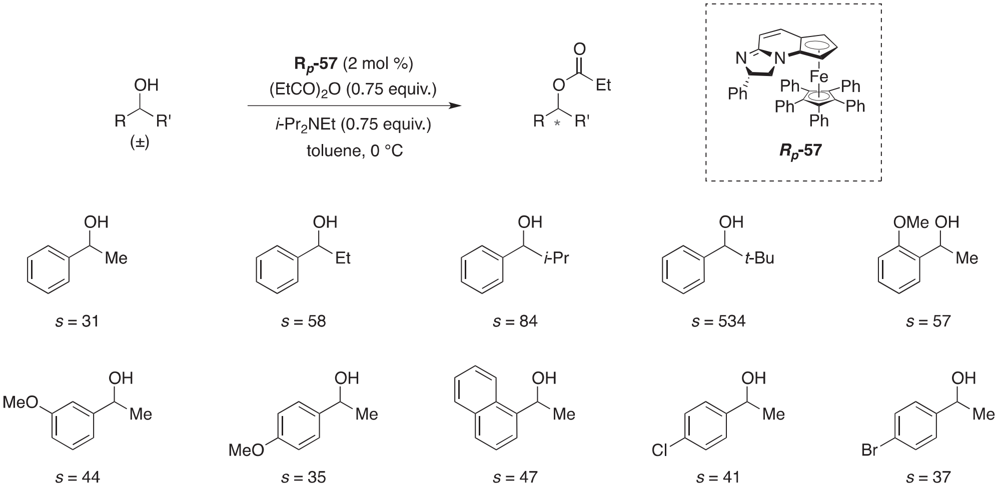
Building upon the results obtained by Birman and coworkers, Smith *et al.* set out to develop an isothiourea-based catalyst that could promote the KR of secondary aryl alkyl alcohols [58]. After screening a range of DHIP catalysts, (2*S*,3*R*)-2-phenyl-3-isopropyl-substituted isothiourea (**56**) proved to be ideal as it afforded high levels of selectivity ($s > 17$) under low catalyst loadings (<1 mol%) (Scheme 41.12). To explain the enantiodiscrimination, the authors proposed a model where the *N*-acylated catalyst adopts a conformation that places the phenyl substituent in a pseudo-axial position to minimize 1,2-strain, resulting in a preferential attack of the (*R*)-enantiomer of the alcohol due to favorable π–π and/or cation–π interactions of the π-system of the alcohol with the acylated isothiouronium catalyst intermediate.

In 2010, Fossey *et al.* developed a new class of planar chiral ferrocene nucleophilic catalysts combining both central and planar chirality [59]. Inspired by Fu's planar chiral DMAP and by Birman's 2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine, R_p-**57** proved to be a remarkably effective catalyst for the KR of various racemic secondary aryl alkyl alcohols, particularly bulky aryl alkyl alcohols, which are usually difficult to resolve. Typically, by performing the reaction in the presence of R_p-**57** (2 mol%), propionic anhydride (0.75 equiv.) and *i*-Pr_2NEt (0.75 equiv.) in toluene at 0 °C, selectivity factors ranging from $s = 31$ for substrates such as α-methyl benzyl alcohol to $s = 534$ in the case of the more bulky α-*tert*-butyl benzyl alcohol could be obtained (Scheme 41.13). Remarkably, the selectivity could be further increased by running the reaction at lower temperatures ($s = 801$ at −20 °C and up to $s = 1892$ at −40 °C), albeit with a concomitant loss in activity.

In the late 1990s, Fuji and Kawabata [19] developed an effective catalyst for the KR racemic alcohols based on an induced-fit mechanism that switches

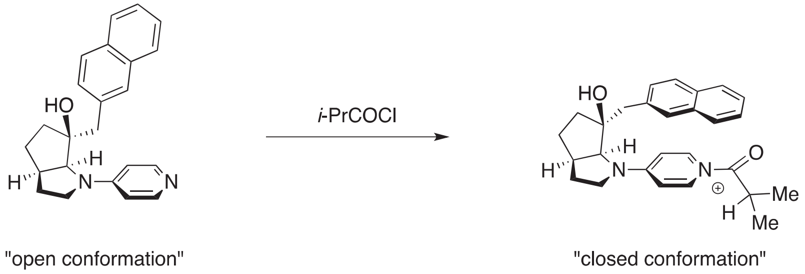


Scheme 41.12 Kinetic resolution of secondary aryl alkyl alcohols by Smith *et al.*

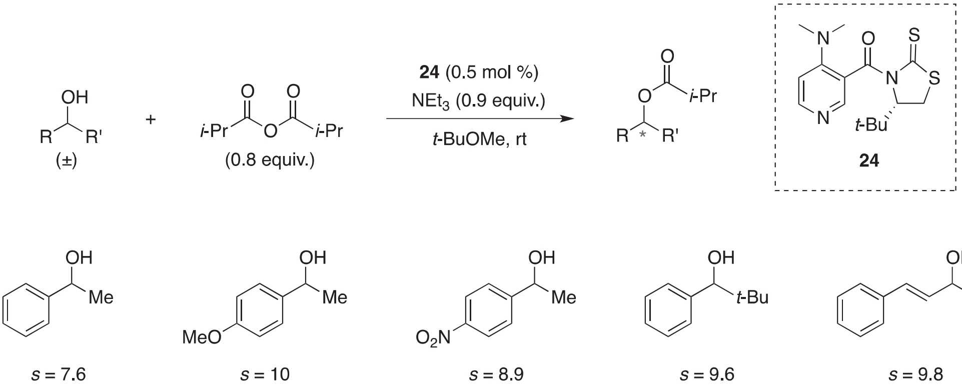


Scheme 41.13 Ferrocene-based planar chiral PIP catalyst for the KR of racemic secondary aryl alkyl alcohols by Fossey *et al.*

the catalyst from an “open” to a “closed” conformation upon activation (Scheme 41.14). Building upon these π–π, cation–π, and related ordering interactions to enhance chirality transfer, Yamada *et al.* [29] developed a new family of chiral catalysts derived from the 4-DMAP scaffold (Figure 41.6) that achieved the KR of a series of secondary alcohols with levels of selectivity ranging from *s* = 7.6 to 10 (Scheme 41.15).



Scheme 41.14 Fuji’s and Kawabata’s catalyst and its acylpyridinium ion.



Scheme 41.15 Kinetic resolution of secondary aryl alkyl alcohols by Yamada *et al.*

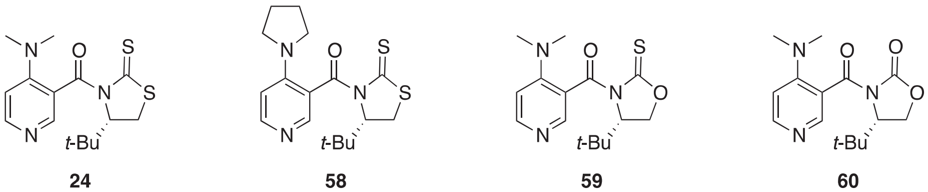
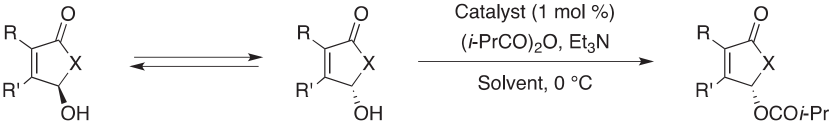


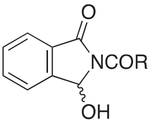
Figure 41.6 Structures of chiral DMAP derivatives developed by Yamada *et al.*

Table 41.1 Dynamic KR of cyclic hemiaminals by Yamada *et al.*

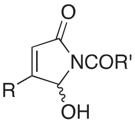


I-VIII

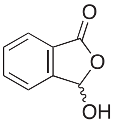
Entry	Substrate	Catalyst	*t* (h)	Solvent	Yield (%)	ee (%)
1	I	24	23	*t*-BuOMe	98	82
2	II	24	11	*t*-BuOMe	>99	84
3	III	24	8	*t*-BuOMe	>99	84
4	IV	24	8	*t*-BuOMe	98	87
5	V	24	23	*t*-BuOMe	95	66
6	III	58	8	*t*-BuOMe	>99	82
7	III	49	8	*t*-BuOMe	99	87
8	III	60	8	*t*-BuOMe	98	70
9	II	24	11	Toluene	99	79
10	II	24	11	CH_2Cl_2	>99	65
11	II	24	11	THF	99	82
12	II	24	11	*c*-Pentyl-OMe	99	84
13	VI	24	8	*t*-BuOMe	94	49
14	VII	24	24	*t*-BuOMe	86	24
15	VIII	24	8	*t*-BuOMe	>99	40



I (R = Me)
II (R = Et)
III (R = *i*-Pr)
IV (R = *t*-Bu)
V (R = Ph)

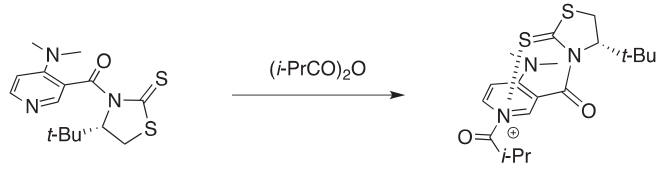


VI (R = Et, R' = Ph)
VII (R = Ph, R' = *i*-Pr)



VIII

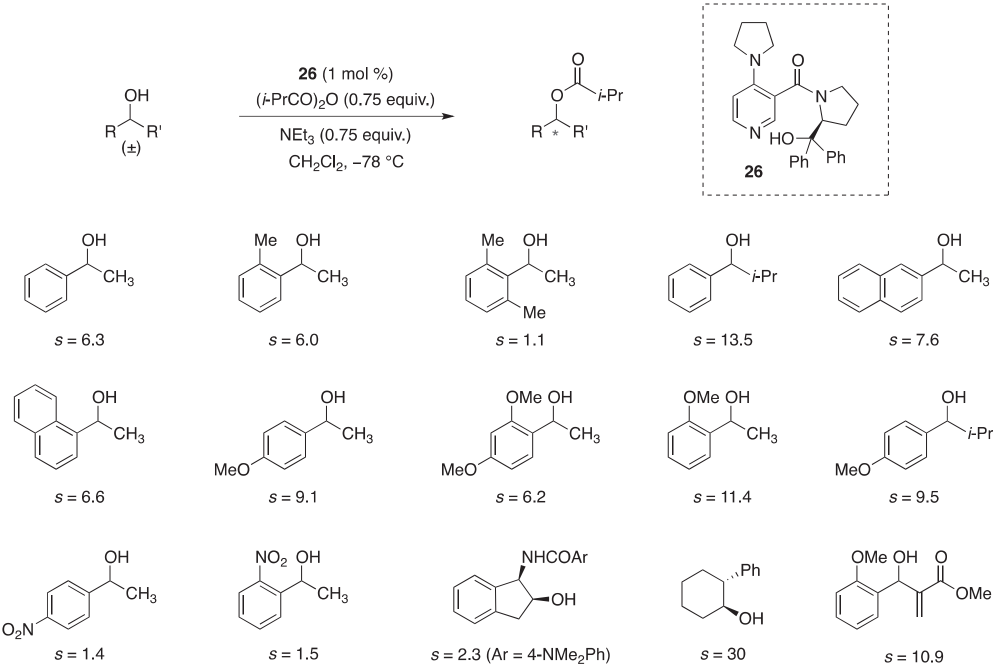
More recently, Yamada *et al.* applied their catalysts to the dynamic KR of cyclic hemiaminals, affording the corresponding esters in excellent yields and particularly high ees (up to 87%) using less than 1 mol% of catalyst (Table 41.1) [60]. The selectivity results from a conformational switch governed by an intramolecular cation–π interaction between the pyridinium ring and the thiocarbonyl group upon N-acylation, which provides a good facial control (Scheme 41.16).



"open conformation" "closed conformation"

Scheme 41.16 Yamada's "conformation-switch" catalyst.

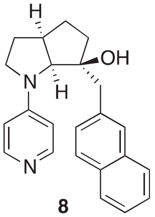
In 2006, Connon *et al.* [61] developed a new class of chiral 4-pyrrolidinopyridine (4-PPY) catalysts, which also operate via an induced-fit mechanism. This new catalyst allowed the attainment of moderate to good selectivities (*s* factors ranging from *s* = 14 to 30) on a wide range of secondary aryl alkyl alcohols, including Baylis–Hillman adducts, which are typically difficult to obtain in an enantiomerically enriched form (Scheme 41.17) [61b].



Scheme 41.17 Kinetic resolution of secondary alcohols using 4-(pyrrolidino)pyridine derivatives by Connon *et al.*

Following their initial discovery that 4-pyrrolidinopyridine-based catalysts such as **61** [19] and later **62** and **63** [19c, d] (Figure 41.7) could induce remote asymmetric induction in the KR of secondary alcohols and in the chemoselective acylation of *meso*-1,3-cyclohexanediol, Kawabata *et al.* extended the use of the 4-PPY framework to the regioselective *O*-isobutyrylation of octyl-β-D-glucopyranoside [62]. Among the four catalysts with dual functional side chains tested (**63**–**66**), catalyst **65** was found to be the most effective for the selective acylation of the secondary hydroxyl group at C4 in the presence of a free primary hydroxyl group at C6 (Table 41.2).

The role of stacking interactions in several of the aforementioned catalyst systems has also been interrogated theoretically using DFT calculations at the SCS-MP2(FC)/6-311 + G(d,p)//MP2(FC)/6-31G(d) level of theory by Zipse *et al.*, who conclude that these interactions can play a decisive role in the stability as well as the conformational preference of many of the acylpyridinium salt transient intermediates [63].



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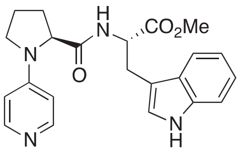

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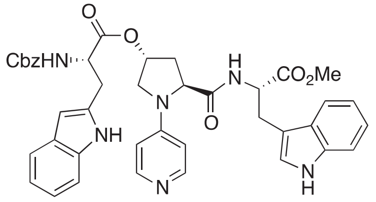

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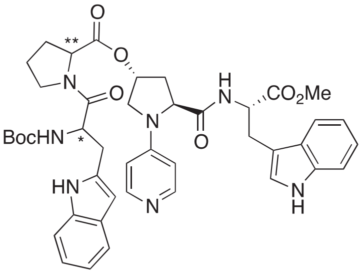
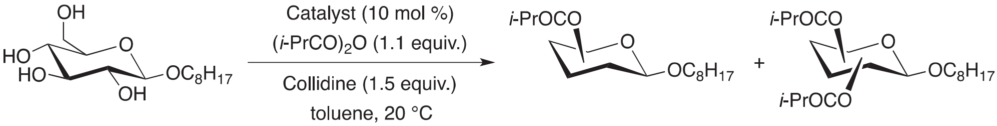


63 (C*,C** = *S*,*S*)
64 (C*,C** = *R*,*S*)
65 (C*,C** = *S*,*R*)
66 (C*,C** = *R*,*R*)

Figure 41.7 Chiral 4-pyrrolidinopyridine analogues developed by Kawabata *et al.* (Cbz = benzyloxycarbonyl).

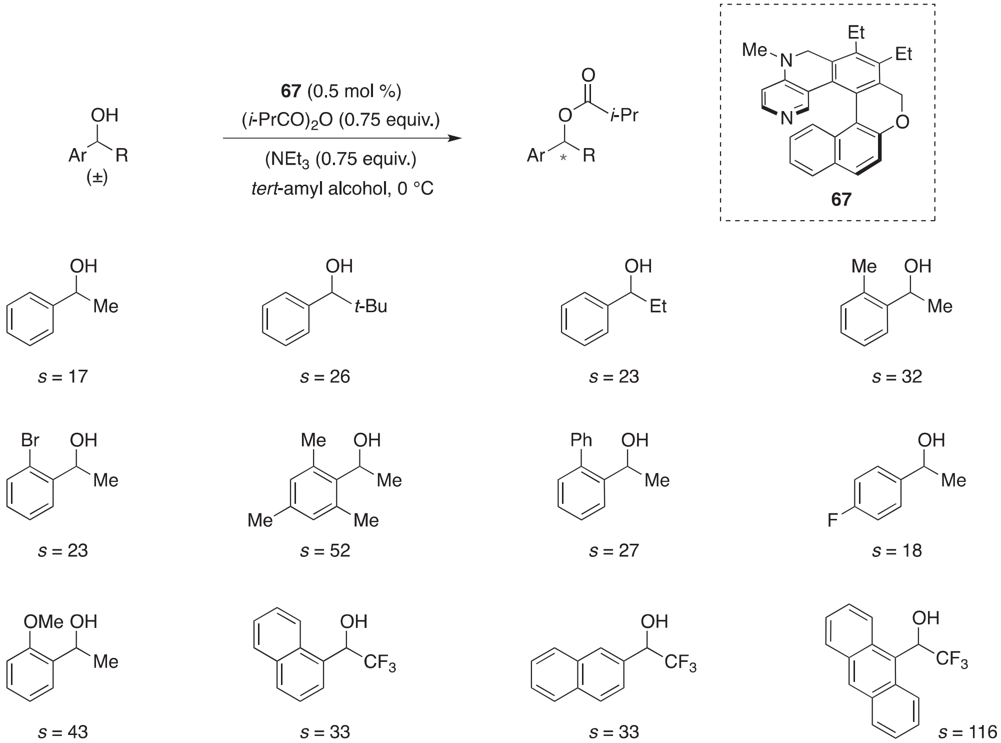
Table 41.2 Effect of catalyst on the regioselective acylation of octyl β-D-glucopyranoside.



Entry	Catalyst	Monoacylation (%)	Regioselectivity (%) 6-*O*/4-*O*/3-*O*/2-*O*	Diacylation (%)	Recovery (%)
1	DMAP	47	36 : 26 : 26 : 12	22	31
2	**63**	66	30 : 60 : 10 : 0	16	16
3	**64**	65	46 : 40 : 11 : 3	20	12
4	**65**	67	56 : 33 : 10 : 1	19	14
5	**65**	62	49 : 39 : 11 : 1	24	10

Carbery *et al.* also used the DMAP scaffold to develop the first helicenoidal asymmetric organocatalyst, which proved to be a particularly selective acylation catalyst for the KR of secondary aryl alkyl alcohols [64]. Catalyst **67** offered good to excellent selectivity factors ranging from $s = 17$ to 116 at catalyst loadings as low as 0.5 mol% (Scheme 41.18).

In 2006, Richards *et al.* reported the synthesis and catalytic evaluation of a new type of DMAP-derivative bearing a metallocene-pyrrolidinopyridine scaffold



Scheme 41.18 Carbery's helicenoidal DMAP catalyst for the KR of secondary aryl alkyl alcohols.

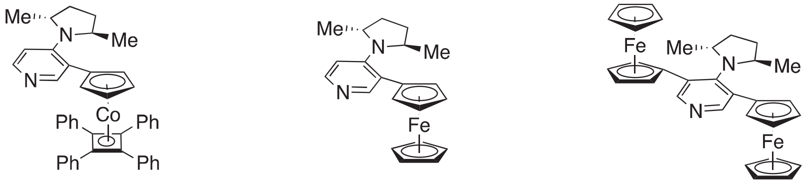


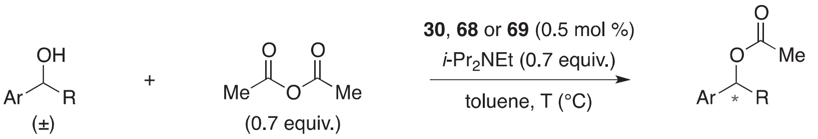
Figure 41.8 Metallocene-pyrrolidinopyridine catalysts developed by Richards *et al.*

(Figure 41.8). 4-Aminopyridine **30**, prepared in three steps starting from commercially available (*S*,*S*)-hexane-2,5-diol, showed promising levels of selectivity in the asymmetric Steglich rearrangement (up to 76% ee at full conversion) but only low activity in the acylative KR of 1-(1-naphthyl)ethanol (*s* factor up to 2.6) [35]. Following these initial results, the same group developed two new metallocene-pyrrolidinopyridine catalysts (**68** and **69**) bearing smaller ferrocene moieties in place of the larger cobalt-based substituent [65]. Both catalysts were evaluated in the KR of secondary aryl alkyl alcohols, but only the *C*2-symmetric (*R*,*R*)-3,5-

diferrocenyl-4-(2,5-dimethylpyrrolidino)pyridine (**69**) induced some enantioselection (up to $s = 6$) (Table 41.3).

Miller *et al.* took a biomimetic approach to design an efficient catalyst for the acylative KR of racemic alcohols that relied on the use of small peptide-based catalysts incorporating an alanine unit as the catalytic core and a *C*-terminal (*R*)-α-methylbenzylamide to eventually favor π–π stacking interactions (Figure 41.9) [22]. The first catalyst of this type to be reported by Miller *et al.* was a tripeptide, which adopted a β-turn type structure with one intramolecular hydrogen bond. Interestingly, replacement of the alanine moiety by the more nucleophilic and less basic histidine unit resulted in higher selectivities in the KR of *trans*-

Table 41.3 KR of secondary aryl alkyl alcohols by Richards *et al.*



Entry	Ar, R	Catalyst	*t* (h)	*T* (°C)	Conversion (%)	ee (%)	*s*
1	Ph, Me	**69** (0.1 mol%)	60	0	52	32	2.5
2	Ph, Me	**69** (0.5 mol%)	24	–40	22	16	4.2
3	Ph, Me	**69** (0.1 mol%)	72	–78	12	9	5.3
4	Ph, Me	**69** (0.5 mol%)	24	–40	8	6	5.8
5	Ph, Me	**69** (0.5 mol%)	24	–40	23	20	6.1
6	Ph, Me	**69** (0.5 mol%)	24	–40	32	25	4.1
7	Ph, Me	**69** (0.5 mol%)	24	–40	79	22	1.3
8	Ph, Me	**69** (0.5 mol%)	24	–40	95	43	1.3
9	*p*-$NO_2C_6H_4$, Me	**69** (0.5 mol%)	11	–40	69	82	5.0
10	*p*-$MeOC_6H_4$, Me	**69** (0.5 mol%)	11	–40	35	18	2.4
11	1-Naphth, Me	**69** (0.5 mol%)	11	–40	79	71	2.7
12	Ph, *t*-Bu	**69** (0.5 mol%)	11	–40	13	6	2.5

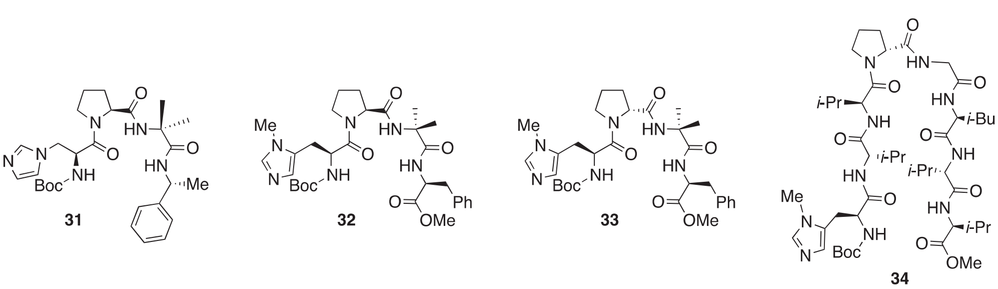
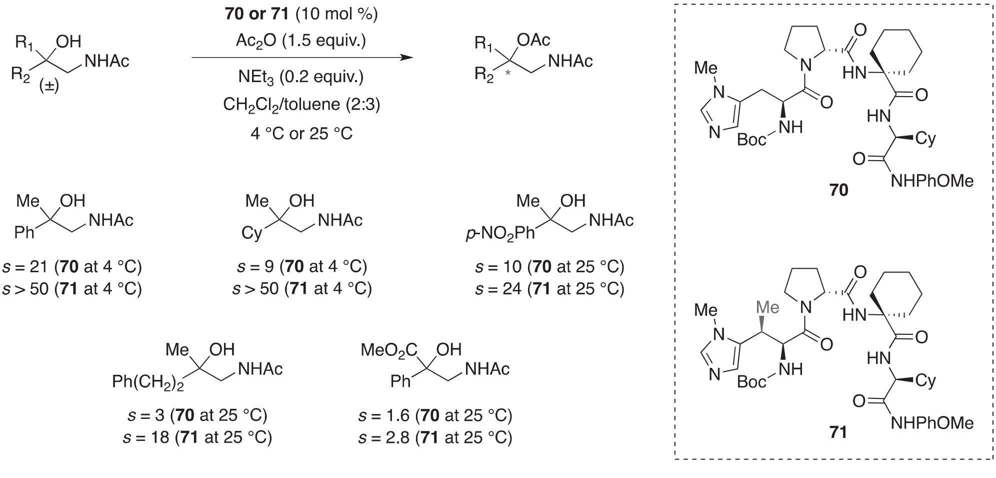


Figure 41.9 Miller's peptide approach to the acylative KR of racemic alcohols.

1,2-acetamidocyclohexanol, while a change in the configuration of the proline (**32** versus **33**) induced a complete reversal of selectivity along with an increase in the level of enantioselection. To demonstrate the importance of the conformational rigidity of the catalyst, a series of octapeptides known to possess four intramolecular hydrogen bonds were synthesized and tested. Among them, (*R*)-proline-containing octapeptide **34** (Figure 41.9) was found to induce high levels of enantioselection ($s = 51$) while its (*S*)-proline analog, which is structurally less well-defined, was substantially less selective ($s = 7$) [22g].

Unfortunately, as none of these catalysts induced useful levels of selectivity in the KR of secondary aryl alkyl alcohols, Miller *et al.* set out to identify specific peptide-catalysts for specific applications using automated peptide synthesis and high-throughput fluorescent screening. This allowed them to unveil some particularly effective catalysts for various transformations such as the KR of an intermediate in the synthesis of aziridomitosane [22h, k], the KR of a series of tertiary alcohols [22i], the regioselective acylation of carbohydrates [22k], and the KR of *N*-acylated *tert*-amino alcohols [22i].

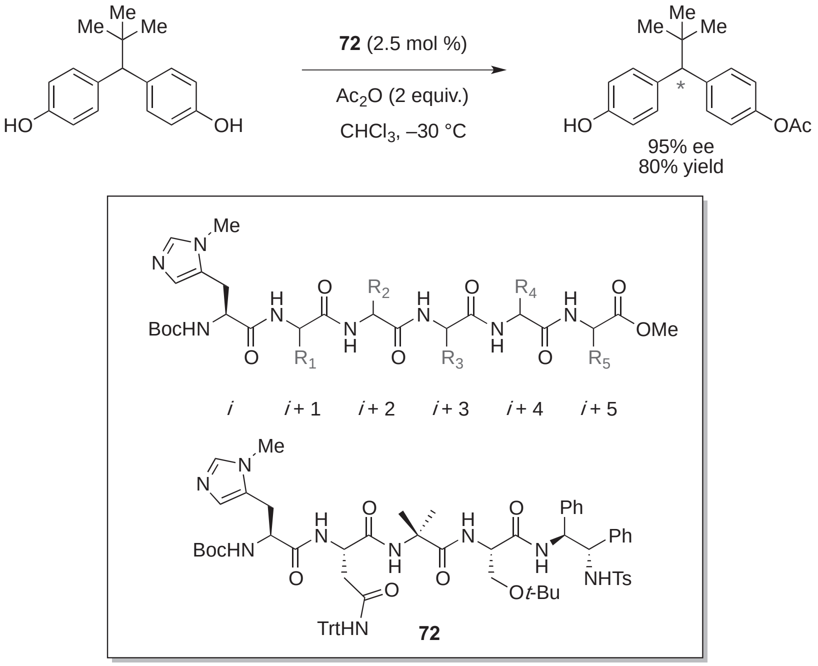
More recently, Miller *et al.* probed the influence of the dihedral angle restriction within a peptide-based catalyst in the KR of tertiary alcohols [66]. This was possible by replacing the π-Me-His unit by a β-Me-π-Me-His (**71**), which resulted in a general increase in selectivity for all the tertiary alcohols tested (Scheme 41.19).



Scheme 41.19 Kinetic resolution of tertiary alcohols by Miller *et al.*

The desymmetrization of bis(phenol) is a difficult synthetic challenge mainly due to the large distance between the two OH groups as well as the large distance between the OH groups and the prochiral stereogenic center. Nonetheless, by screening a library of peptides, Miller and coworkers were able to identify peptide

72 as an effective catalyst for the monoacetylation of bis(phenol) affording the desired product in 80% yield and 95% ee, which compared favorably with enzymatic methods (Scheme 41.20) [67].

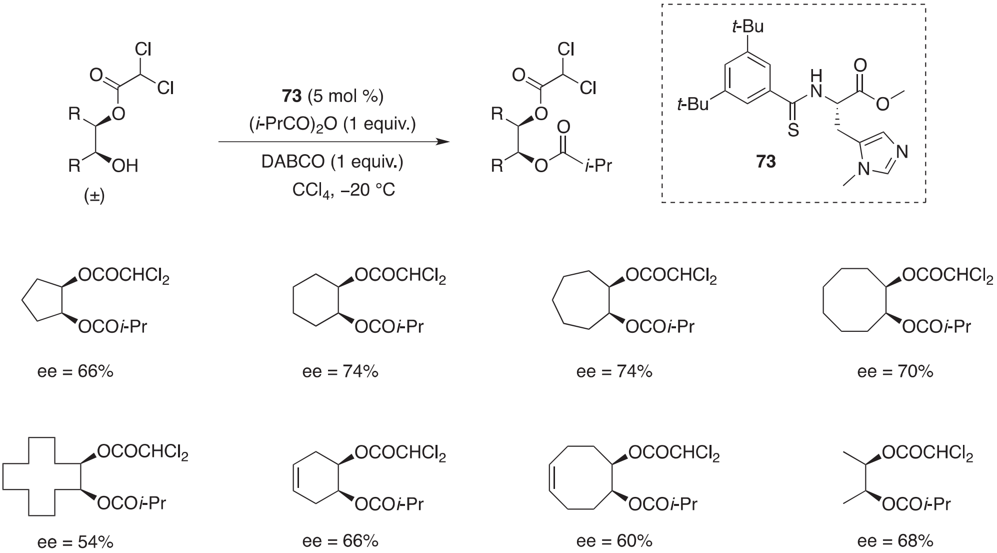


Scheme 41.20 Desymmetrization of remote diols by peptide-catalyzed acylation [Trt = trityl (triphenylmethyl)].

A similar π-methyl histidine-based strategy was chosen by Qu *et al.* in their quest to develop a low molecular weight catalyst for the KR of racemic secondary alcohols [68]. Hence, after screening a series of catalysts bearing a methyl histidine moiety, *N*-thiobenzoyl-1-methylhistidine methyl ester **73** was found to be a particularly efficient catalyst for the KR of monoprotected *cis*-diols as well as terminal vicinal diols.

Based upon these results, catalyst **73** was also used in the dynamic KR of racemic monoacylated dichloroacetates. This method, which relies on the rapid *in situ* racemization of the substrate in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) through dichloroacetoxy migration, resulted in high enantioselectivities, ranging from 54% to 74%, and excellent yields (Scheme 41.21) [69].

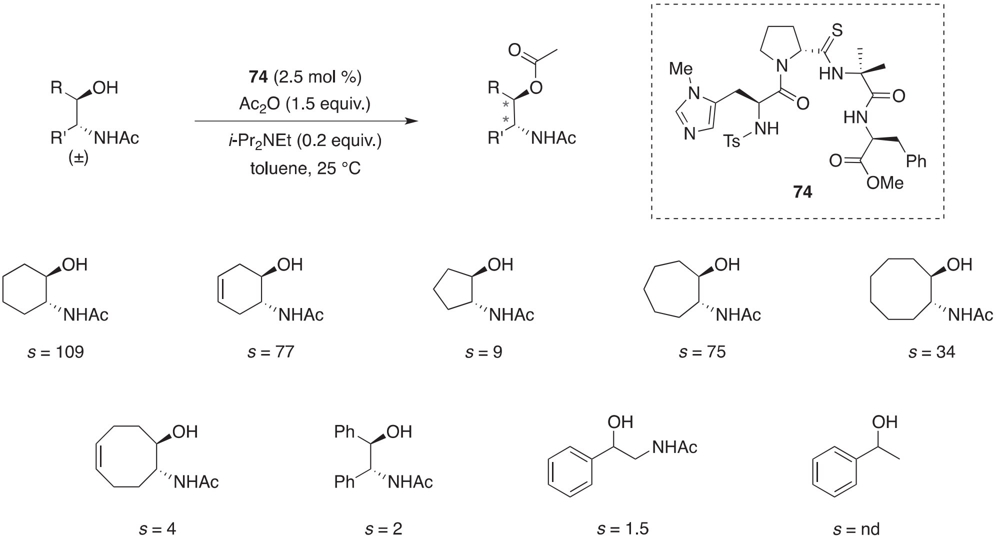
By using combinatorial screening, Qu *et al.* found that compound **74**, which only differs from Miller's tetrapeptide **32** by the presence of a thioamide and a sulfonamide that confer a more constrained β-hairpin conformation, afforded



Scheme 41.21 Desymmetrization of *meso*-1,2-diols via dynamic KR by Qu *et al.*

higher selectivities in the acylative KR of *trans*-2-(*N*-acetylamino)carbinols, resulting in selectivity factors ranging from $s = 1.5$ to 109 (Scheme 41.22) [70].

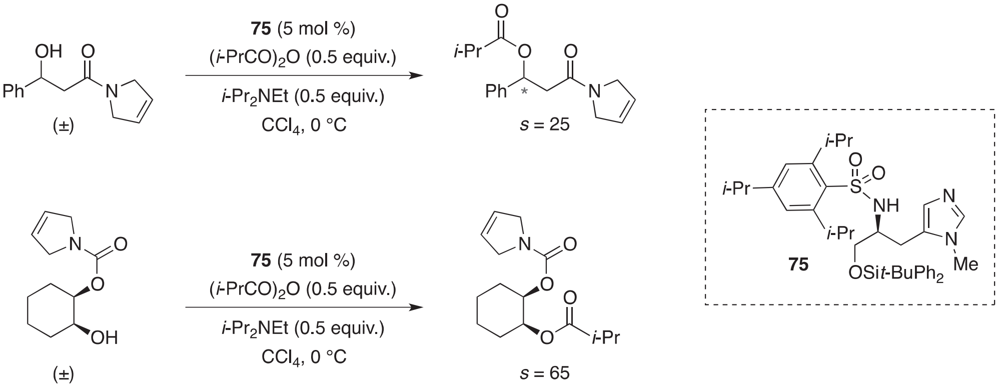
Inspired by Miller's biomimetic approach, Ishihara *et al.* [28] developed a "minimal artificial acylase" derived from (*S*)-histidine for use in the KR of mono-protected *cis*-1,2-diols and *N*-acylated 1,2-amino-alcohols. Interestingly, Ishihara's



Scheme 41.22 Kinetic resolution of *trans*-2-(*N*-acetylamino)carbinols by Qu *et al.*

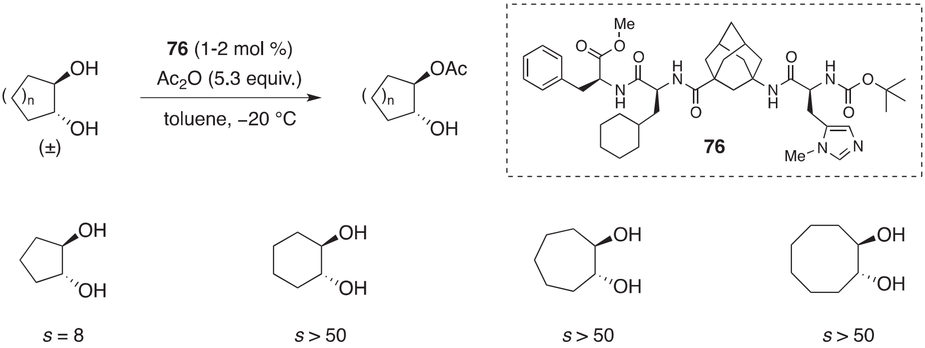
catalyst **75** contains only one stereogenic center and incorporates a sulfonamide linkage in place of the polypeptide chain to promote H-bonding with the substrates, but still achieved high levels of selectivity for a wide variety of racemic alcohols.

More recently, Ishihara *et al.* [71] developed a particularly useful protecting group for the KR of α- and β-hydroxycarboxylic acids, 1,2-dicarboxylic acids, and 1,2-diols. The 3-pyrroline-1-carbonyl protecting group is not only easily removable under mild conditions but can also improve selectivity during the KR process by participating through hydrogen bonding with the sulfonamidyl proton (Scheme 41.23).



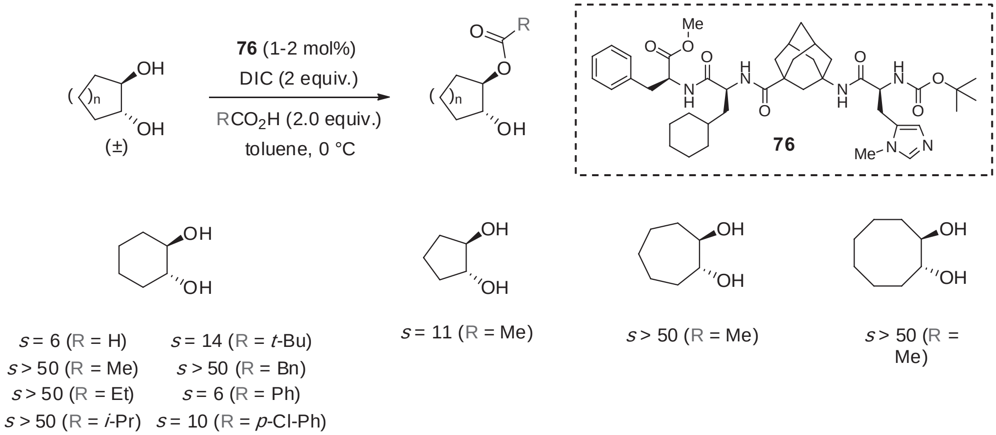
Scheme 41.23 3-Pyrroline-1-carbonyl protecting group by Ishihara *et al.*

In 2008, Schreiner *et al.* reported the use of peptide **76** in the KR of racemic *trans*-cycloalkane-1,2-diols [72]. Interestingly, the structure of **76** includes a rigid non-natural γ-aminoadamantane motif, which precludes any internal hydrogen bonding known to secure conformational rigidity. Nonetheless, this new class of peptide-catalyst allowed attainment of moderate to good selectivities in the case of six-, seven- and eight-membered ring *trans*-cycloalkane-1,2-diols (Scheme 41.24).



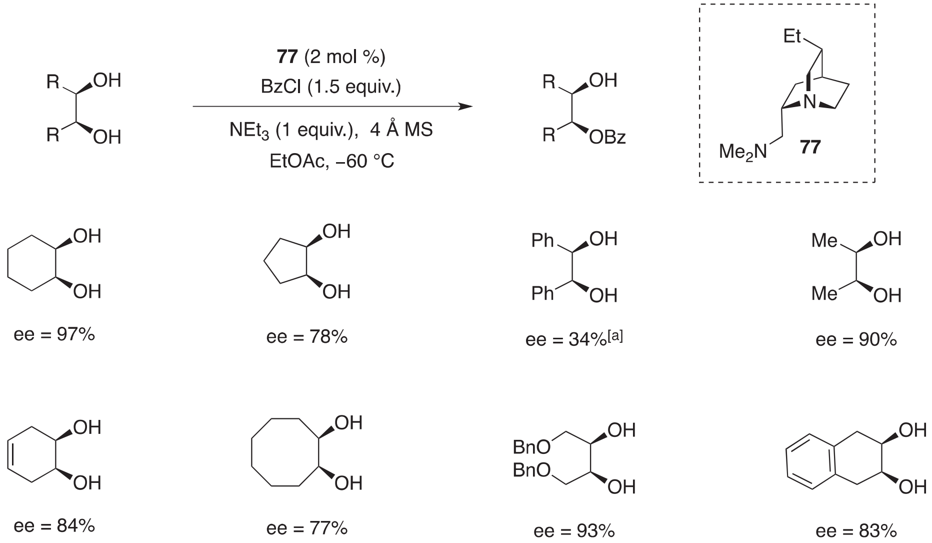
Scheme 41.24 Kinetic resolution of *trans*-cycloalkane-1,2-diols by Schreiner *et al.*

Schreiner *et al.* also reported the use of catalyst **76** in conjunction with various carboxylic acids for the enantioselective Steglich esterification of *trans*-cycloalkane-1,2-diols [73]. The reaction, which proceeds through the *in situ* formation of an anhydride, affords high levels of selectivity (*s* ranging from 6 to >50) and prevents the use of unstable or difficult to access anhydrides (Scheme 41.25).



Scheme 41.25 Enantioselective Steglich esterification by Schreiner *et al.* (DIC = diisopropylcarbodiimide).

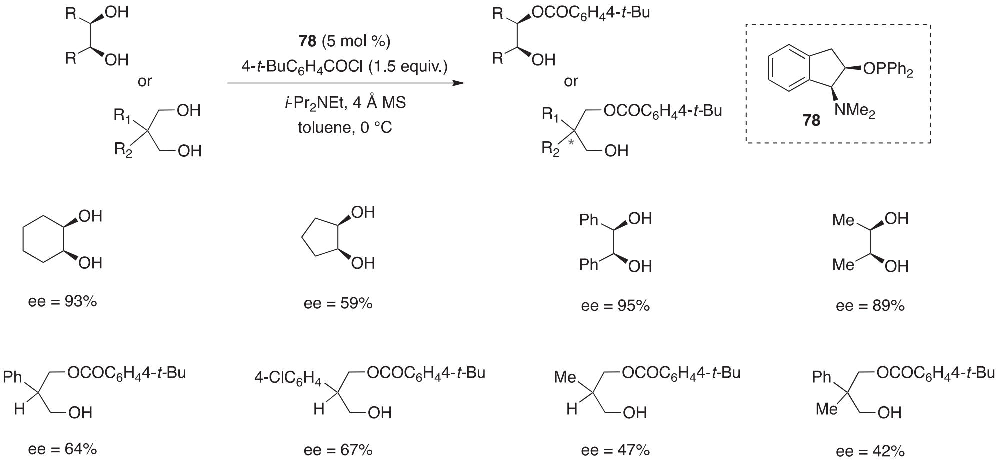
In 2008, Kündig *et al.* [74] developed a low molecular weight quincorine-derived chiral catalyst for the asymmetric monobenzoylation of cyclic and acyclic *meso* 1,2-diols, affording ees ranging from 34% to 97% (Scheme 41.26). The rationale behind the design of their catalyst relied on the use of two tertiary amine moieties, one of which would function as an acyl activator while the



Scheme 41.26 Desymmetrization of *meso* 1,2-diols by Kündig *et al.* [a] Reaction run in THF.

second one would be engaged in a selective hydrogen bonding with one of the two hydroxy groups.

More recently, Fujimoto *et al.* developed an easily accessible aminophosphinite-type catalyst (**78**), which was found to be particularly effective for the ASD of *meso* 1,2-diols, affording the corresponding monoesters in up to 95% ee (Scheme 41.27) [75]. Prepared in three steps starting from commercially available *cis*-aminoindanol, this Brønsted–Lewis dibasic bifunctional organocatalyst was also shown to selectively acylate *meso*-1,3-diols albeit with slightly lower ees (Scheme 41.27).

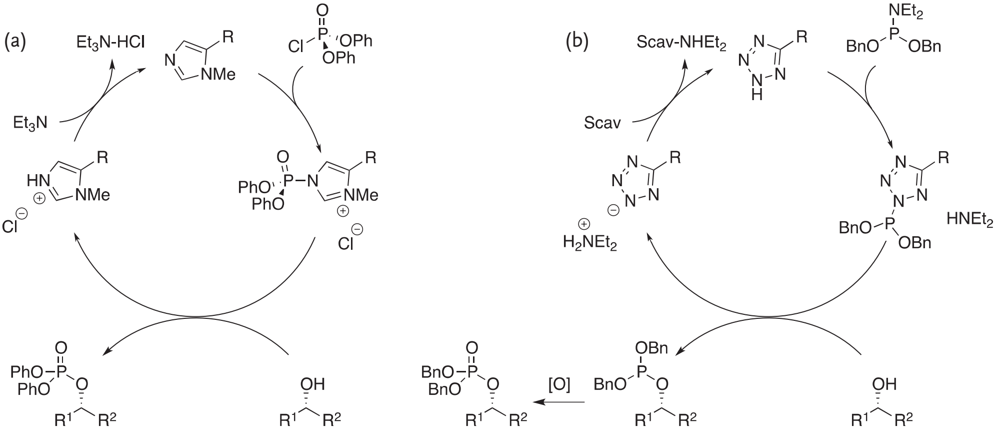


Scheme 41.27 Desymmetrization of *meso* 1,2- and 1,3-diols by Fujimoto *et al.* (MS = molecular sieves).

41.2.2
Phosphorylation-Based Process

By comparison with alcohol asymmetric acylation (i.e., esterification) as discussed above, alcohol asymmetric phosphorylation has not attracted so much attention from the synthetic community thus far. This is rather curious given the pivotal importance of phosphorylated alcohols in biological systems where three of the most important and well-studied signal transduction pathways, the mitogen-activated protein kinase pathway (MAPK), adenylyl cyclase dependent pathway (cAMP), and inositol triphosphate/diacylglycerol pathway (IP_3/DAG), all rely critically on chemo- and/or stereoselective alcohol phosphorylation/dephosphorylation by kinase/phosphatase enzymes, respectively [76].

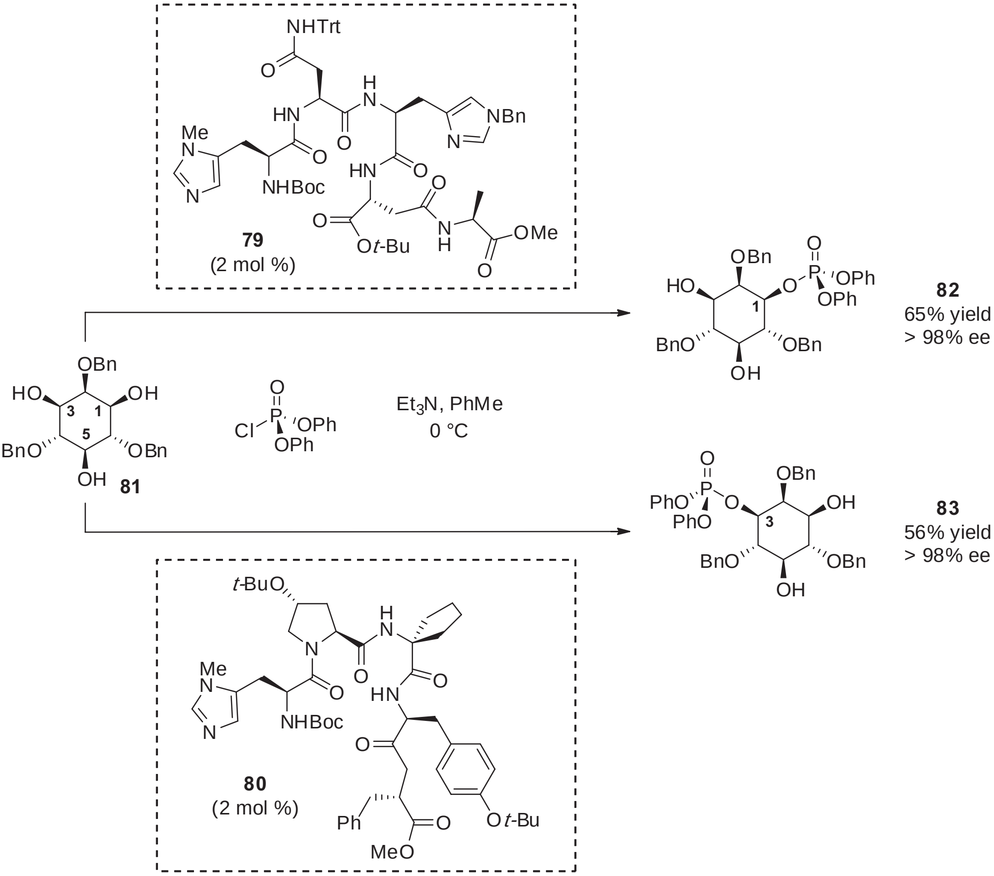
Although the process of direct phosphoryl transfer shares some mechanistic similarities to acyl transfer in so far as it can be catalyzed by some of the same small-molecule nucleophiles (e.g., *N*-methylimidazole, 4-DMAP, pyridine-*N*-oxides) [77], it presents some distinct challenges with regard to *asymmetric* catalysis as the result of the tetrahedral nature of the transferred phosphorus(V) center as compared to the trigonal planar carbonyl carbon. Additionally, *achiral* alcohol phosphorylation is more commonly performed via phosphitylation using a phosphorus(III) reagent (e.g., a phosphoramidite) followed by oxidation rather than by direct phosphoryl transfer. This is because phosphorus(V) reagents (e.g., phosphoryl chlorides, pyrophosphates) are generally regarded as being less reactive and less synthetically versatile, with respect to ease of incorporating bespoke phosphoester protecting groups, as compared to phosphorus(III) reagents. Additionally, while promotion of alcohol phosphitylation by small-molecule nucleophilic catalysts (e.g., tetrazole) is well established, particularly in the synthesis of RNA (ribonucleic acid) and DNA (deoxyribonucleic acid) [78], the nucleophiles that are efficient for phosphorus(III) transfer are structurally and functionally distinct from those for phosphorus(V) and acyl transfer. This is because catalysts for phosphorus(III) transfer are protic and bifunctional: they initially act as a Brønsted acid protonating the phosphoramidite and then the corresponding conjugate base effects nucleophilic substitution/activation at the phosphorus(III) center. It follows that the protic catalyst must be regenerated for turnover. When using phosphoramidates, this does not usually occur spontaneously following the alcohol phosphitylation step because the liberated dialkylamine is generally protonated in preference to the catalyst. As a consequence, most "nucleophilic" catalysts for alcohol phosphitylation are deployed in stoichiometric or greater quantities, although 10 Å MS [79] and most recently isocyanates [80] have been described for scavenging dialkylamines to facilitate efficient catalyst turnover in this context (Scheme 41.28).



Scheme 41.28 Comparison of the catalytic cycles for "nucleophile" phosphorylation via (a) direct phosphorylation with a phosphoryl chloride [i.e., a P(V) reagent]; (b) phosphitylation with a phosphoramidite [i.e., a P(III) reagent], then oxidation (Bn = benzyl).

Undoubtedly as a consequence of the different catalyst characteristics and turnover requirements for phosphitylation as compared to phosphoryl and acyl transfer, catalytic asymmetric variants have only very recently emerged for phosphitylation (see below), and all the initial work towards developing efficient asymmetric phosphorylation centered on direct phosphorylation of alcohols using phosphoryl chlorides.

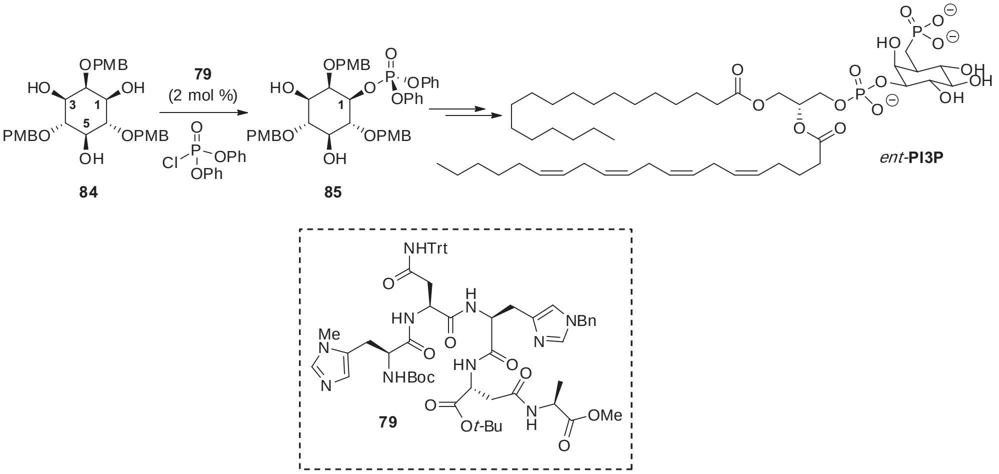
The Miller group was the first to report catalytic asymmetric phosphorylation of alcohols, in 2001 [81]. They reported that D-*myo*-inositol-1-phosphate **82** could be prepared with high levels of enantiomeric purity by the ASD of 2,4,6-tribenzyl-*myo*-inositol (**81**) using diphenyl(chloro)phosphate and triethylamine in toluene at 0 °C catalyzed by 2 mol% of pentapeptide **79**, which contains an *N*-terminal π-methyl histidine residue as the nucleophile (Scheme 41.29).



Scheme 41.29 Asymmetric desymmetrization of a *myo*-inositol derivative by Miller *et al.*

Subsequently, they demonstrated that the enantiomeric product D-*myo*-inositol-3-phosphate **83** could be prepared with an equivalent level of enantioselectivity (>98% ee) and similar yield (**83**, 56% versus **82**, 65% yield) by using a different peptide (**80**) containing the same catalytic π-methyl histidine residue but notably incorporating a 4-hydroxyproline residue (Hyp) at the *i* + 1 position and a

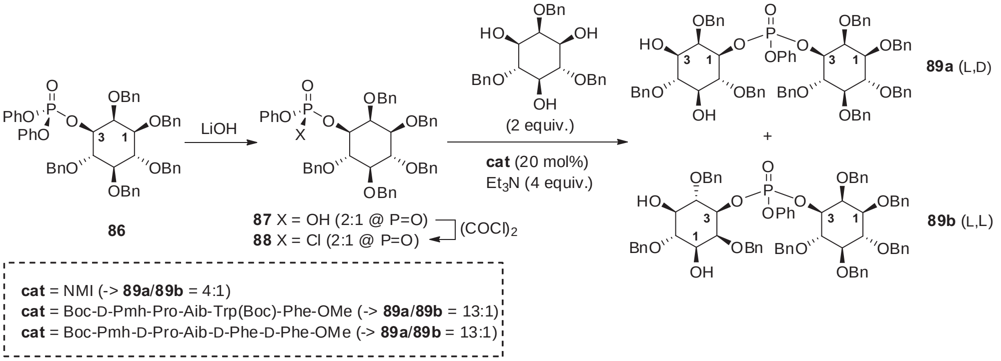
1-amino-1-carboxycyclopentane residue (Sp5) at the *i* + 2 position [82, 83]. They went on to demonstrate that an equally efficient ASD of D-*myo*-inositol derivative **81** could be achieved at room temperature using just 1 mol% of catalyst **79** on a preparative scale, allowing for the synthesis of various phosphatidylinositol-3-phosphates with saturated and unsaturated side chains [84]. However, synthesis of the unsaturated natural product *ent*-PI3P required using 2,4,6-tri(PMB)-*myo*-inositol **84** as the substrate for ASD (Scheme 41.30).



Scheme 41.30 Synthesis of *ent*-PI3P via phosphorylative ASD by Miller *et al.* (PMB = *para*-methoxybenzyl).

Building on this work, Miller *et al.* showed that 2-*O*-benzyl-4,6-bis(PMB)-D-*myo*-inositol was a versatile orthogonally protected substrate for the synthesis of various inositol di-, tri-, and tetraphosphates of importance in signaling studies [85, 86], that selected deoxygenated congeners could be accessed by incorporating Barton-type radical deoxygenation into the reaction schemes [87], and, moreover, that phosphatidylinositols [88], for example, phosphatidylinositol-5-phosphate-DiC8 and its enantiomer, could be prepared using this approach [89].

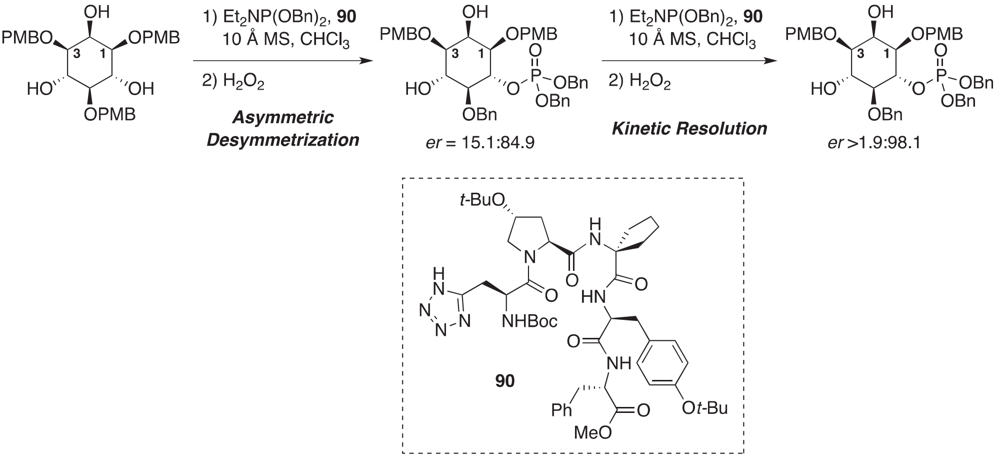
In all the aforementioned pioneering work by the Miller group, diphenylphosphoryl chloride was employed as the phosphorylating agent for ASD and invariably this necessitated "transesterification" of the resulting phosphate triester derivative to allow for subsequent synthetic manipulations (e.g., using NaH, BnOH to give the corresponding dibenzyl ester). The use of dibenzylphosphoryl chloride directly in the ASD process is precluded by competitive S_N2-type debenzylation [87] and in any case synthesis of pure chlorophosphates with other ester substituents is sometimes problematic [90]. However, selective mono-hydrolysis of the diphenyl phosphate triester products can be achieved (using LiOH, THF–H_2O) and following re-activation as a chlorophosphate [using $(COCl)_2$, DMF] this opens up the possibility of carrying out a second peptide-catalyzed asymmetric phosphorylation using another inositol. This leads to a fascinating and complex situation given that the chlorophosphate is obtained as an inseparable mixture of diastereoisomers at the phosphorus(V) center and the resulting phosphorylation process is subject to double-diastereomeric induction (i.e., both the catalyst stereochemistry and the substrate chemistry influence the stereochemical outcome of the coupling process: matched/mismatched combinations can be expected). In the event, Miller *et al.* found that the substrate bias of the coupling stereochemistry could be strongly influenced by the choice of catalyst employed [e.g., from **89a** (L-/D-)/**89b** (L-/L-) = 4 : 1 using an achiral *N*-methylimidazole (NMI) promoter to either 13 : 1 or 1 : 2.5 depending on the chiral pentapeptide deployed]. Interestingly, the most successful peptide catalysts, as judged by their ability to override the substrate bias, were not those optimized in the above studies (i.e., peptides **79** and **80**) but rather new ones found by re-screening (still containing the *N*-terminal π-methyl histidine) [91]. This work led to an efficient approach to L,D- and L,L-di-*myo*-inositol-1,1′-phosphates, which are known to exhibit intriguing behavior as natural intracellular stabilizers in hyperthermophilic microorganisms at extreme temperatures and enabled a pioneering study of their relative abilities to stabilize relevant enzymes (Scheme 41.31) [88].



cat = NMI (-> **89a**/**89b** = 4:1)
cat = Boc-D-Pmh-Pro-Aib-Trp(Boc)-Phe-OMe (-> **89a**/**89b** = 13:1)
cat = Boc-Pmh-D-Pro-Aib-D-Phe-D-Phe-OMe (-> **89a**/**89b** = 13:1)

Scheme 41.31 Synthesis of L,D- and L,L-di-*myo*-inositol-1,1′-phosphates by Miller *et al.* (NMI = *N*-methylimidazole).

To circumvent the aforementioned limitations associated with the nature of the phosphate ester substituents that are currently compatible with nucleophilic catalysis of phosphorus(V) transfer, the Miller *et al.* recently disclosed their preliminary findings in developing analogous processes for phosphorus(III) transfer [92]. Specifically, they developed tetrazole-functionalized peptide **90** that, in combination with 10 Å MS in chloroform at room temperature, can catalyze the ASD of 2,4,6-tri(PMB)-*myo*-inositol using dibenzyl(diethylamino) phosphoramidite; the dibenzyl-phosphate product is obtained following oxidative workup with hydrogen peroxide (Scheme 41.32).



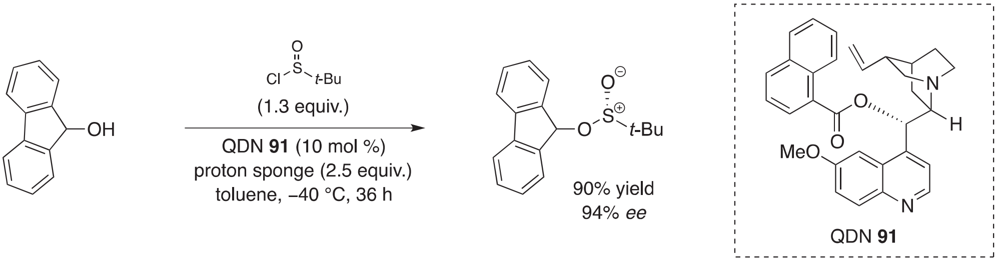
Scheme 41.32 The first catalytic asymmetric phosphitylation/oxidation of an inositol derivative by Miller *et al.* (er = enantiomeric ratio).

In particular, it is notable that by using this catalytic manifold Miller *et al.* were able to distinguish between the 4 and 6 positions of a D-*myo*-inositol derivative, a task for which good selectivity had apparently proved elusive in the phosphorus(V) transfer manifold. Successful discrimination between enantiomers, even with these tetrazole-containing catalysts, did, however, require the reactions to be completed as a sequential asymmetric ASD and then KR so as to exploit H-bonding interactions between the catalyst and the phosphate oxygen during the second step.

Most recently, Miller *et al.* have exploited the tolerance of their phosphitylation protocol to variation of substituents on the phosphoramidite to allow incorporation of an *ortho*-iodobenzyl ether substituent. Use of this phosphoramidite allows for a subsequent radical deoxygenation step, making the overall process one of targeted hydroxyl group deoxygenation [93]. Further exciting developments of this chemistry can undoubtedly be expected in the near future. Already, as mentioned earlier, progress has been made to develop alternative secondary amine scavengers for use in phosphitylation processes [80].

41.2.3
Sulfonylation- and Sulfinylation-Based Process

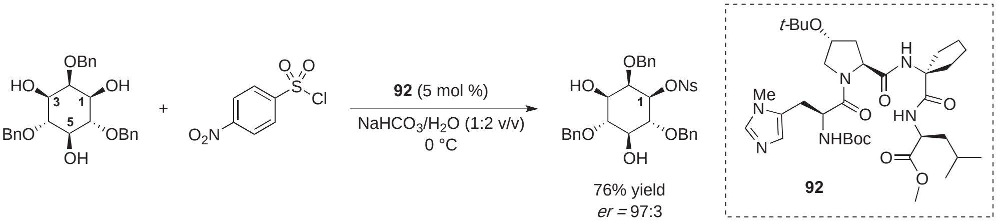
Catalytic asymmetric sulfonylation and sulfinylation of alcohols has received even less attention than phosphorylation. Early work addressed the sulfinylation of achiral primary alcohols using racemic sulfinyl chlorides catalyzed by nucleophilic chiral amines with a view to effecting dynamic KR (DKR) of the sulfinyl stereogenic center and delivering enantiomerically highly enriched sulfinate esters, which are valuable precursors to chiral sulfoxides and sulfinamides. Although diastereoselective and non-catalytic variants of this process are well established, the first efficient catalytic enantioselective process was developed by Miller and Ellman *et al.* in 2004 [94]. They found that an octapeptide containing an *N*-terminal N-Boc-π-methylhistidine residue (2 mol%) was able to mediate the sufinylation of benzyl alcohol by *tert*-butanesulfinyl chloride with concomitant DKR in THF at −78 °C over 40 h in the presence of proton sponge [1,8-bis(dimethylamino)naphthalene] to yield the sulfinate ester product in essentially quantitative yield and 80% ee. Ellman subsequently reported screening several additional chiral amine nucleophilic catalysts with known activity as acyl transfer catalysts for this same transformation and found that quinidine (10 mol%) was also an efficient catalyst in the presence of proton sponge, providing the product in quantitative yield and 87% ee in toluene after 20 h at −78 °C [95]. The use of 2,4,6-trichlorobenzyl alcohol in place of benzyl alcohol and switching to THF as solvent afforded product in 90% ee. Contemporaneously, Shibata *et al.* developed a very similar protocol employing quinidine-1-naphthoate **91** as the nucleophilic catalyst (10 mol%), *tert*-butanesulfinyl chloride, proton sponge, and using 9-fluorenol as the alcohol in toluene at −40 °C for 36 h. This delivered the product in 90% yield and 94% ee (Scheme 41.33) [96].



Scheme 41.33 Dynamic KR of *tert*-butane sulfinyl chloride using a quinidine derivative by Shibata *et al.* (QDN = quinidine-1-naphthoate).

Catalytic asymmetric sulfonylation, which is clearly more directly comparable with the above-described work involving KR and ASD of racemic secondary alcohols and 1,2-diols by acylation and phosphorylation, has received attention only very recently. Some work has been carried out by Onomura *et al.* into catalytic ASD of *meso*-1,2-diols by monosulfonylation [97] and the sulfonylative KR of racemic 2-hydroxyalkanamides [98, 99] catalyzed by chiral copper-BOX type Lewis acids, but only one report by the Miller group addresses nucleophile-catalyzed asymmetric sulfonylation.

In 2009, Miller *et al.* explored the extension of their studies using π-methyl histidine-containing peptides as nucleophilic catalysts for group transfer reactions to the *mono*-sulfonylation of *myo*-inositol derivatives by aryl sulfonyl chlorides. Catalyst screening identified tetrapeptide derivative **92** as being efficient for distinguishing the enantiotopic secondary alcohol groups at the 1- and 3-positions when the reactions were performed in biphasic Schotten–Baumann-type conditions consisting of CH_2Cl_2/aqueous $NaHCO_3$ at 0 °C. Under optimized conditions the mono-nosylate could be obtained in 76% yield and with an er of 97 : 3 and similarly successful desymmetrizations were achieved on various related *myo*-inositols (Scheme 41.34) [100].



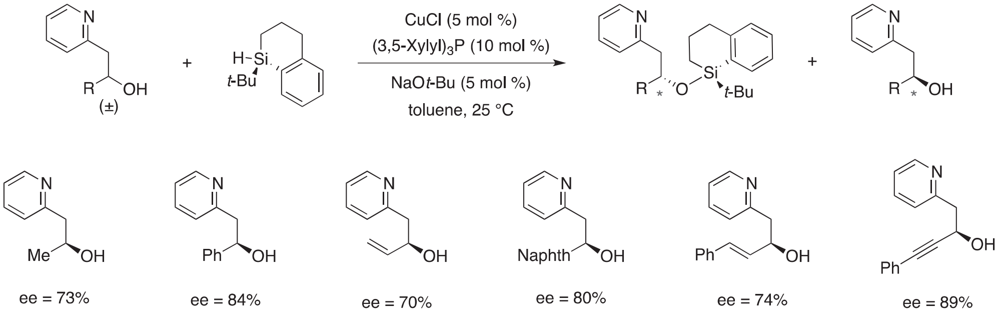
Scheme 41.34 Sulfonylative catalytic ASD of a *myo*-inositol derivative by Miller *et al.*

Intriguingly, Miller *et al.* noted that the sense of induction in these *myo*-inositol ASD sulfonylations was opposite to that observed in the corresponding phosphorylations when employing catalysts having ostensibly the same structural features. In particular, peptides having a common L-4-hydroxyproline residue at the $i + 1$ position (e.g., peptide **80**, Scheme 41.29; cf. peptide **92**, Scheme 41.34) catalyze stereodivergent outcomes in sulfonylative versus phosphorylative ASD reactions, despite the fact that the chirality of this residue has previously been shown to nucleate the type of β-turn adopted in these peptides. Clearly, further work is required to tease out the mechanistic and/or conformational origins of these differences; work that is likely to lead to further insight into the detailed mode of chirality transfer in these important reactions.

41.2.4
Silylation-Based Process

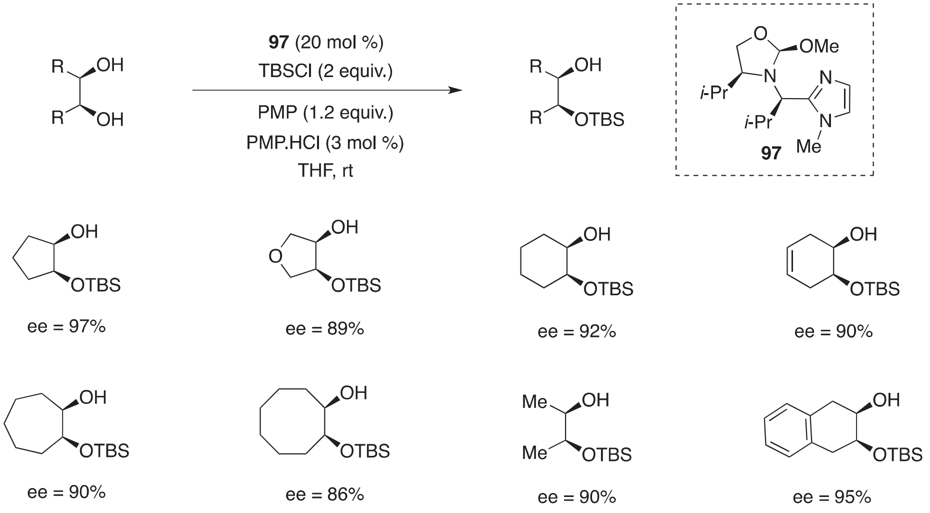
Since the pioneering work of Ishikawa *et al.* [101], silylation-based KR of alcohols has become an active area of research, resulting in the discovery of some particularly useful processes [102].

Oestreich *et al.*, for example, reported a Cu-catalyzed KR of 2-pyridyl-substituted benzylic secondary alcohols using a chiral trialkylsilyl hydride (stereogenic at Si), which undergoes preferential σ-bond metathesis with one of the enantiomeric copper(I)-alkoxide chelates [103]. Interestingly, not only could this reagent-controlled KR process lead to promising levels of selectivity (ee of the slow-reacting alcohol ranging from 73% to 89%) but both the chiral-resolving reagent and the fast-reacting ether could be recovered racemization-free after reductive cleavage of the silyl ether (Scheme 41.35).



Scheme 41.35 Kinetic resolution of secondary alcohols by dehydrogenative coupling with recyclable silicon-stereogenic silanes.

In the same year, Tan *et al.* [104] also developed an efficient catalyst for the silylation-based desymmetrization of *meso* 1,2-diols. Based on a reversible covalent bonding strategy, their catalyst incorporated a substrate-binding site as well as a catalytically active residue (imidazole moiety). Among all the catalysts tested (Figure 41.10), compound **97** appeared to be the most selective, affording the monosilylated product in high ees ranging from 86% to 97% at room temperature (Scheme 41.36).



Scheme 41.36 Highly enantioselective desymmetrization of *meso* 1,2-diols by Tan *et al.*

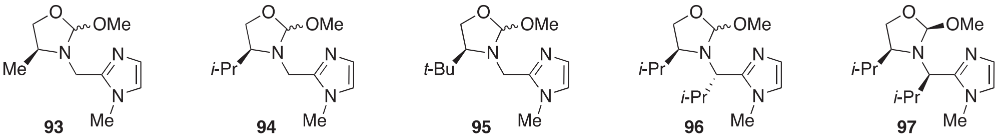
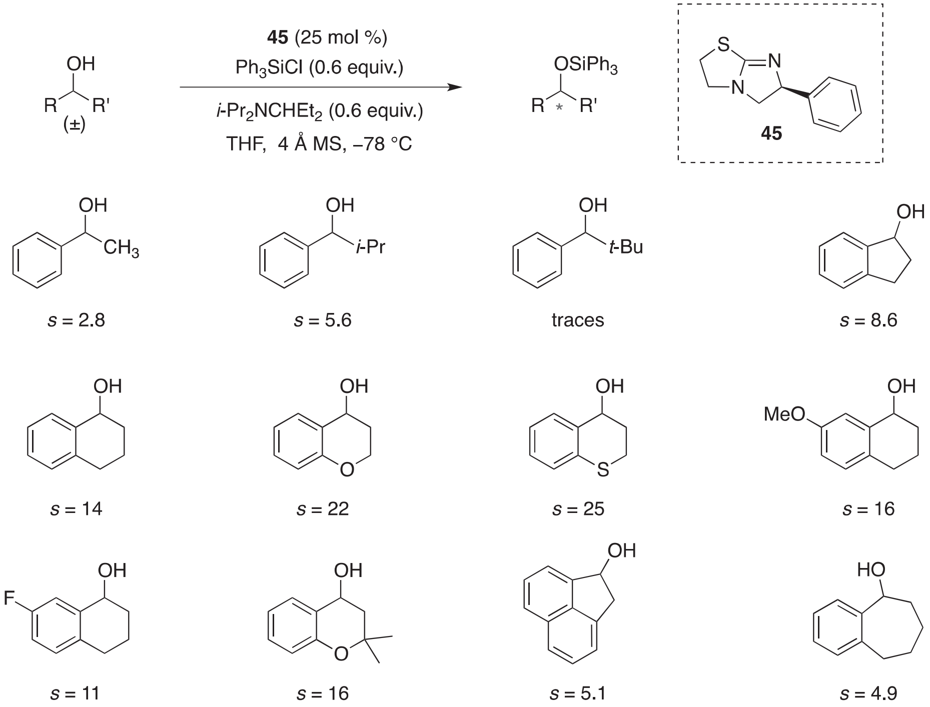


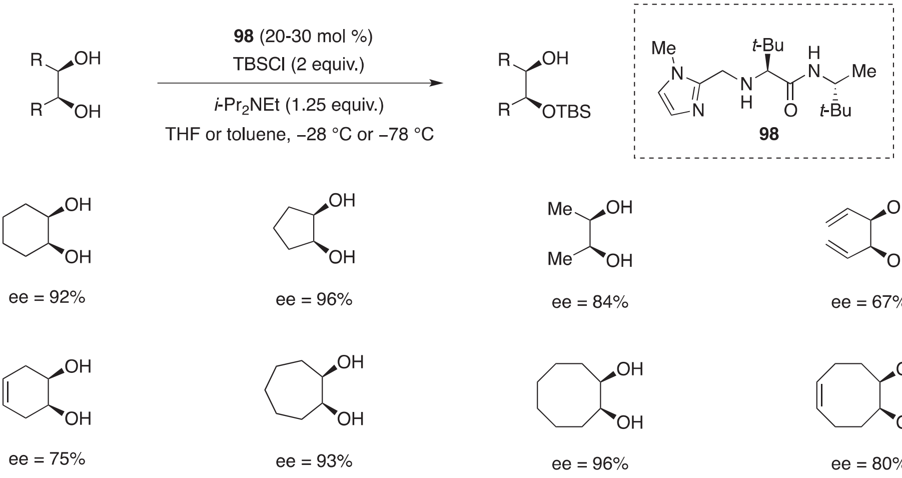
Figure 41.10 Enantioselective silylation catalysts developed by Tan *et al.*

More recently, Wiskur *et al.* [105] found that tetramisole **45** could also catalyze the KR of secondary alcohols via enantioselective silylation. Hence, after fine-tuning the silyl donor (Et_3SiCl < $Me_2PhSiCl$ < $Ph_2MeSiCl$ < Ph_3SiCl), the nature of the solvent (polar, coordinating solvents such as THF gave the highest selectivities) and the base (non-nucleophilic, sterically hindered bases such as *N*,*N*-diisopropyl-3-pentylamine gave the best results), Wiskur *et al.* were able to resolve a range of cyclic secondary alcohols with moderate to good selectivities ranging from $s = 4.9$ to $s = 25$. Unfortunately, acyclic secondary alcohols proved to be more difficult, affording only low to moderate levels of selectivity ($2.8 < s < 5.6$) (Scheme 41.37).



Scheme 41.37 Silylation-based KR of secondary alcohols by Wiskur *et al.*

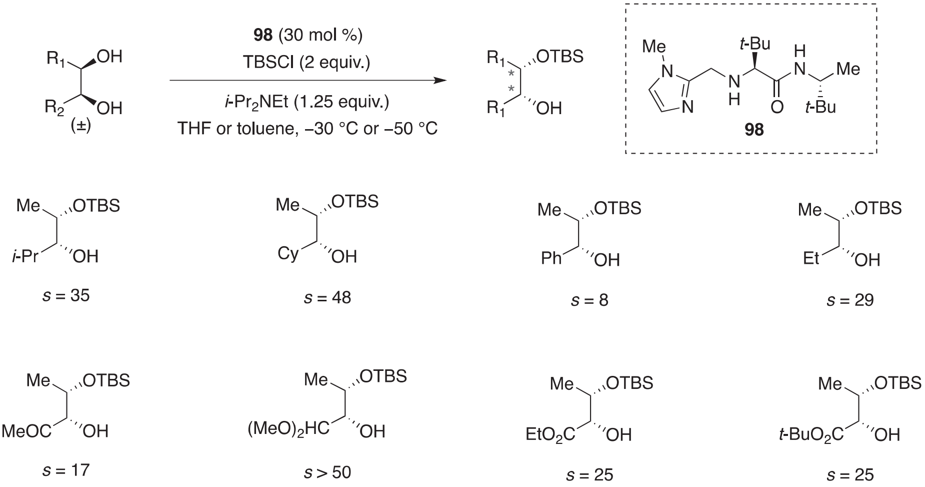
Hoveyda, Snapper *et al.* [106] evaluated several amino-acid-based small molecules in the silylation-based desymmetrization of *meso* 1,2-diols. Their strategy solely relied on the incorporation of a Lewis basic moiety, which is likely to increase the electrophilicity of the silyl halide reagent [107], and potential H-bonding sites. Among the catalysts tested, compound **98** appeared to be the most effective, affording the corresponding monosilylated products with up to 96% ee (Scheme 41.38).



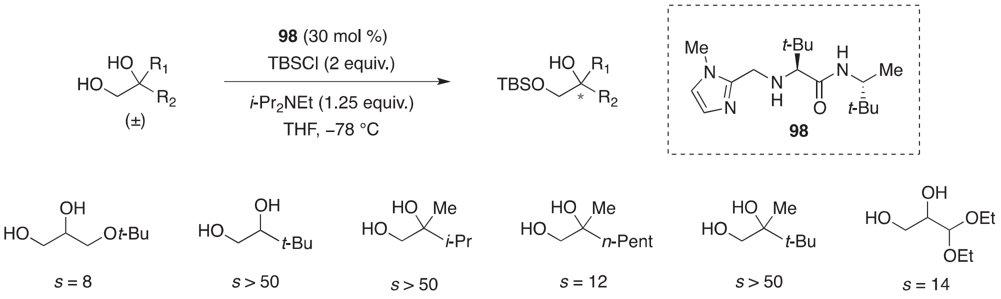
Scheme 41.38 Catalytic enantioselective silylation of *meso* diols by Snapper *et al.*

Racemic diols, in particular those bearing a primary alcohol adjacent to a secondary or a tertiary carbinol, which are traditionally more difficult to resolve, were also shown to be viable substrates for catalyst **98** [108]. Indeed, high levels of selectivity ranging from $s = 8$ to >50 were obtained independently of the substitution pattern (Schemes 41.39 and 41.40).

Hoveyda and Snapper *et al.* [109] eventually developed conditions for the KR of diols bearing sterically and electronically similar substituents. Hence, by running the reactions in the presence of 30 mol% of catalyst **98** and 1.5 equiv. of either

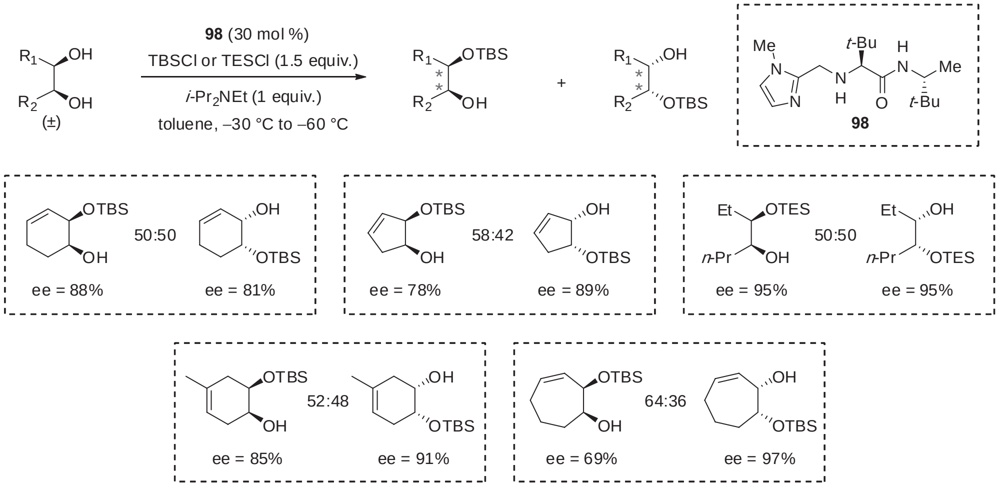


Scheme 41.39 Kinetic resolution of secondary alcohols by catalytic asymmetric silylation.



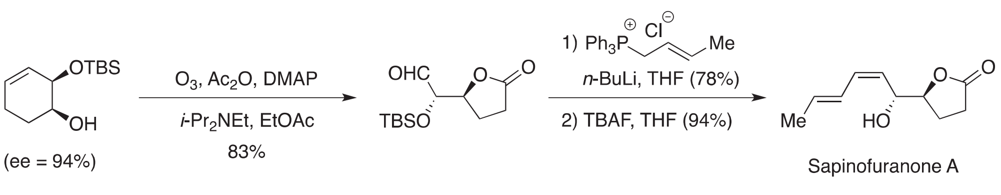
Scheme 41.40 Kinetic resolution of 1,2-diols by catalytic asymmetric silylation.

TBSCl or TESCl, the racemic diols were successfully converted into the regioisomeric, enantiomerically enriched, monosilylated products (Scheme 41.41).



Scheme 41.41 Regiodivergent reactions through catalytic enantioselective silylation of chiral diols by Snapper, Hoveyda *et al.*

The synthetic utility of this method was eventually highlighted in the first total synthesis of sapinofuranone A, a natural product isolated from the liquid cultures of the phytotoxic fungus *Sphaeropsis sapinea* by Evidente *et al.* in 1999 (Scheme 41.42) [110].



Scheme 41.42 Synthesis of sapinofuranone A by Snapper and Hoveyda *et al.* (TBAF = tetrabutylammonium fluoride).

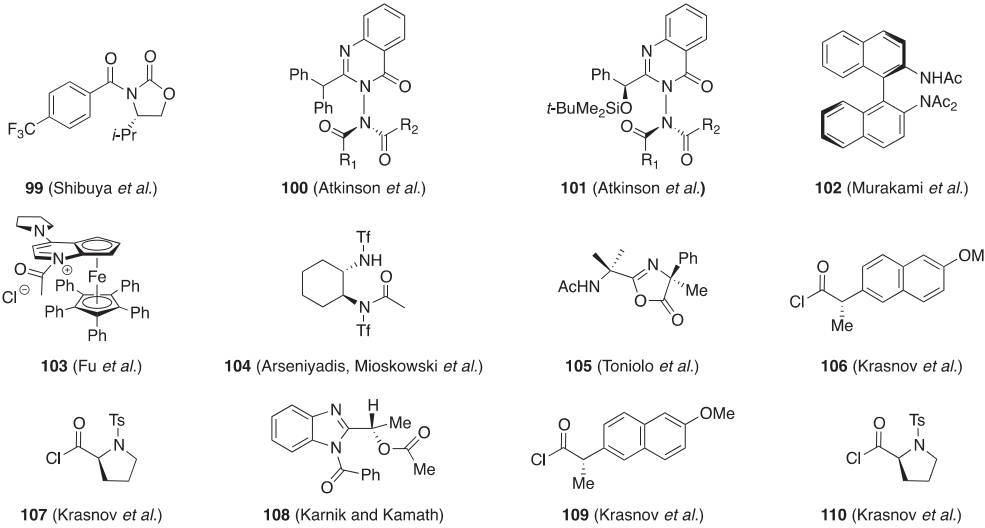
41.3
Kinetic Resolution of Amines

Chiral amines are another important class of molecules due to their interesting biological properties and ubiquitous nature [111]. Interestingly, however, while the design of enantioselective acyl transfer reagents and catalysts for the KR of alcohols is particularly well documented, the development of a general and effective non-enzymatic KR process for racemic amines remains a particularly challenging field of research.

During the past two decades, several particularly efficient methods have been reported for the stereoselective acylation of racemic amines using stoichiometric amounts of chiral acylating agents, notably by Shibuya [112], Atkinson [113], Murakami [114], Krasnov [115], Fu [18t], Arseniyadis and Mioskowski [116], Toniolo [117] and more recently by Karnik and Kamath [118] (Figure 41.11). As these methods have already been thoroughly documented in previous reviews [9, 10, 119], again our discussion here focuses exclusively on the latest developments, which have resulted in some promising catalytic systems for the KR of certain classes of racemic amine.

41.3.1
Acylation-Based Process

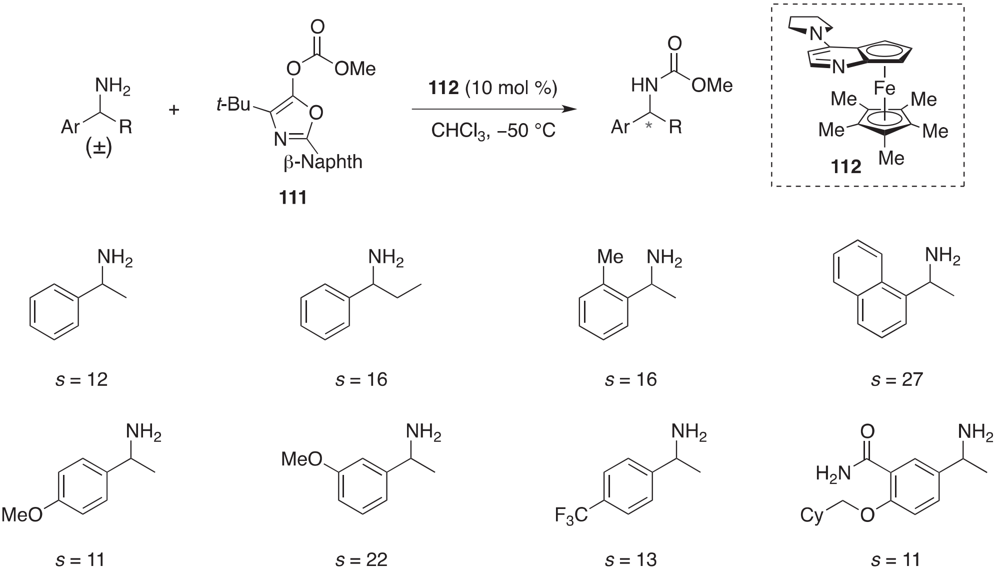
Over the past few years, the design of enantioselective acyl transfer catalysts suitable for use with amines has become a major focus for the synthetic community. This endeavor has been particularly challenging due to the high nucleophilicity of most amines toward typical acylating agents, thus requiring a fine-tuning of the reactivity of the chiral selector to enable chiral induction.



99 (Shibuya *et al.*)
100 (Atkinson *et al.*)
101 (Atkinson *et al.*)
102 (Murakami *et al.*)
103 (Fu *et al.*)
104 (Arseniyadis, Mioskowski *et al.*)
105 (Toniolo *et al.*)
106 (Krasnov *et al.*)
107 (Krasnov *et al.*)
108 (Karnik and Kamath)
109 (Krasnov *et al.*)
110 (Krasnov *et al.*)

Figure 41.11 Example of reagents for the KR of racemic amines.

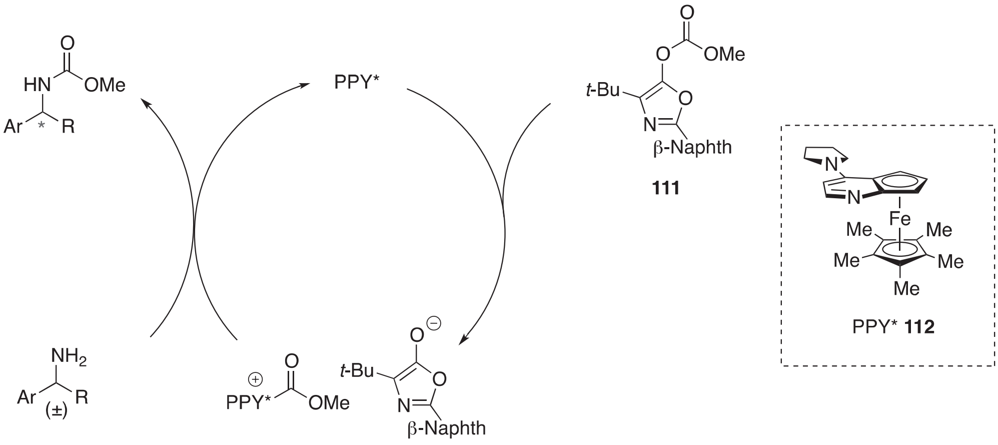
Fu *et al.* were the first to develop an efficient catalytic system for the KR of primary amines [120]. Their method relied on the use of a stoichiometric amount of the *O*-acylated azlactone **111** as the achiral acyl donor in conjunction with a catalytic amount of a planar chiral DMAP derivative **112.** Hence, after optimizing the reaction conditions, they were able to resolve various racemic primary aryl alkyl amines with moderate to good selectivities ranging from *s* = 11 to 27 independently of the substitution pattern on the aromatic ring or on the alkyl chain (Scheme 41.43).



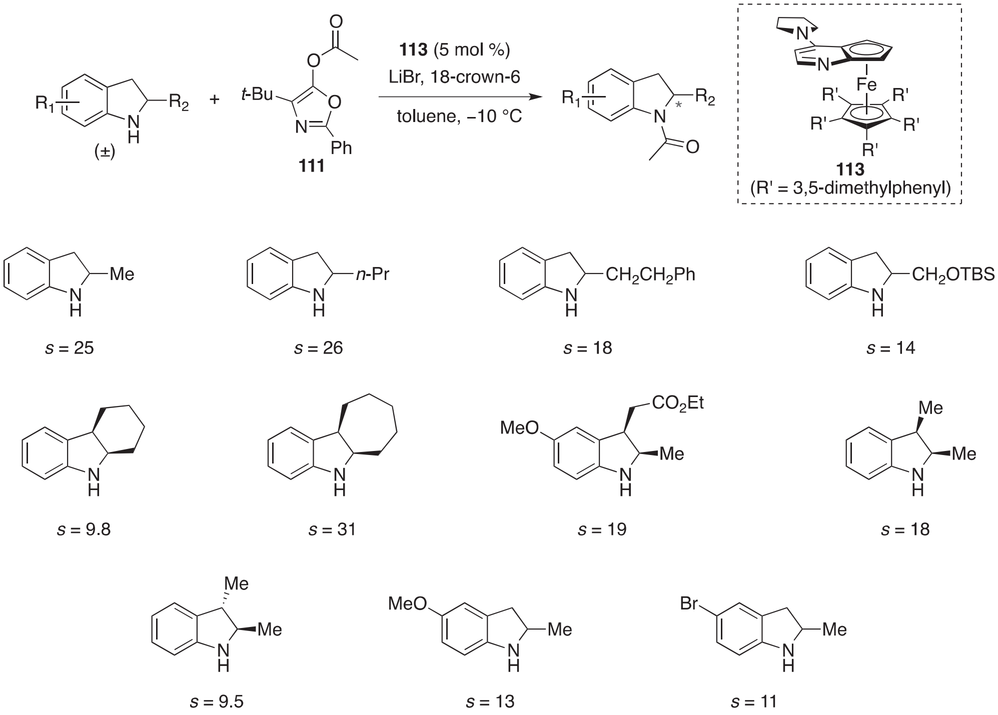
Scheme 41.43 Fu's planar ferrocenyl DMAP catalyzed KR of primary aryl alkyl amines.

The mechanism proposed by the authors involved the rapid formation of a transient acyl pyridinium species (ion-pair) followed by a slow transfer of the methoxycarbonyl group to the amine (stereo-determining step) to afford the corresponding enantio-enriched carbamate (Scheme 41.44).

The scope of the method was later extended to indolines [121]; however, as the previous optimized conditions failed to afford any acylated product, a fine-tuning of both the nucleophilic catalyst and the acyl donor appeared to be necessary. After intensive screening, the use of a bulkier cyclopentadienyl-derived catalyst such as **113** in conjunction with *O*-acetylated azlactone **111** led to a more effective catalytic system, allowing the resolution of various indolines with useful levels of selectivity ranging from *s* = 9.5 to 31 (Scheme 41.45). Most importantly, 2,3-disubstituted indolines, which are usually difficult to obtain in high ee by other methods such as the asymmetric hydrogenation of indoles, were also shown to be suitable substrates.

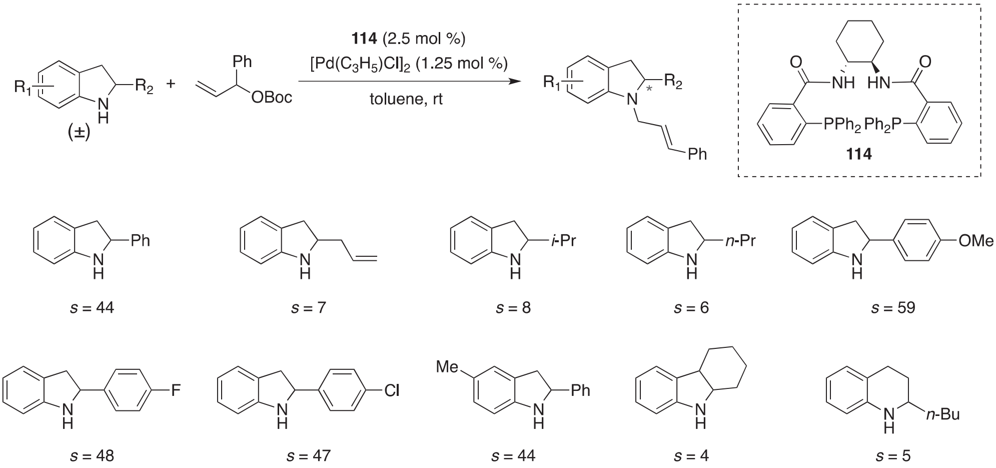


Scheme 41.44 Proposed mechanism for the KR of amines catalyzed by **112**.



Scheme 41.45 Fu's planar ferrocenyl DMAP catalyzed KR of indolines.

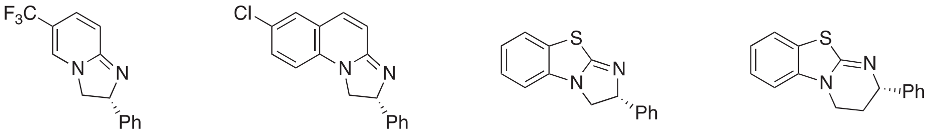
In 2009, Hou and Zeng showed that an asymmetric palladium-catalyzed allylic alkylation reaction could also be used for the KR of amines [122]. Hence, in the presence of Trost's chiral ligand **114** (2.5 mol%) and a branched allylic carbonate, indolines were resolved in both high yields and high selectivities, with *s*-factors ranging from *s* = 4 to 59 (Scheme 41.46). Interestingly, this was the first example of KR involving a transition-metal-catalyzed allylic substitution reaction.



Scheme 41.46 Hou's palladium-catalyzed asymmetric allylic alkylation strategy for the KR of indolines.

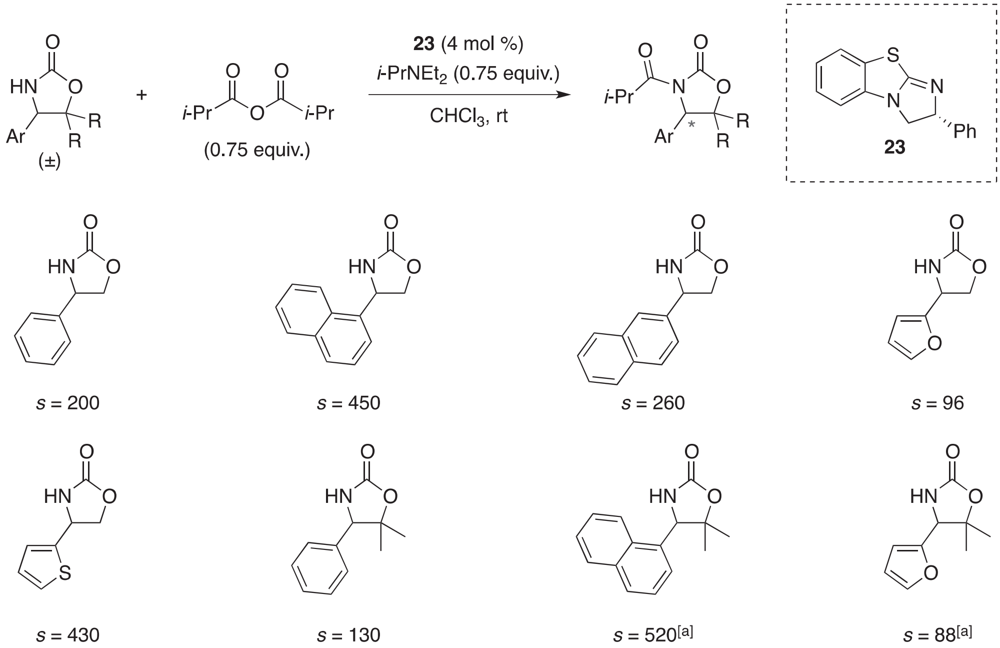
In 2006, Birman and coworkers showed that dihydroimidazo[1,2-*a*]pyridine (DHIP) derivatives, such as CF_3-PIP **20** and Cl-PIQ **22**, as well as isothioureas such as benzotetramizole (BTM, **23**) and HBTM (**47**) could serve as effective chiral catalysts for the acylative KR of racemic oxazolidinones [123]. These catalysts, which rely on π–π and cation–π interactions and which had already been successfully used in the enantioselective acylation of benzylic alcohols, showed impressive selectivities in the case of 4-aryl- and 4-heteroaryl-substituted 2-oxazolidinones (Figure 41.12).

As a general trend, BTM (**23**) was shown to induce markedly higher selectivities, allowing the resolution of various 4-substituted 2-oxazolidinones at room temperature with selectivity factors up to *s* = 520 (Scheme 41.47).



CF_3PIP **20** Cl-PIQ **22** BTM **23** HBTM **47**

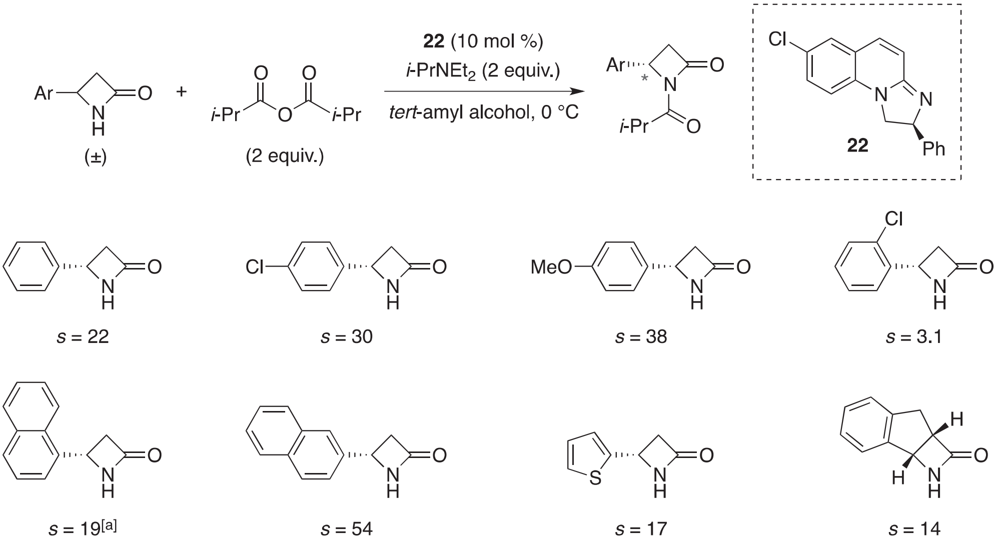
Figure 41.12 Birman's catalysts for the KR of 2-oxazolidinones.



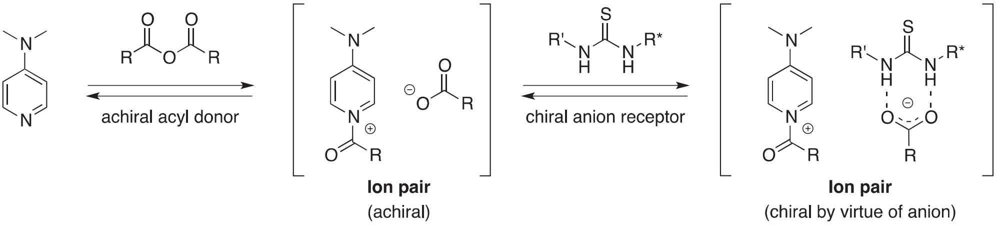
Scheme 41.47 Birman's benzotetramizole-based KR of 2-oxazolidinones. [a] 1.5 equiv. of $(i\text{-PrCO})_2O$ and 0.75 equiv. of $i\text{-Pr}_2NEt$ and 8 mol% of **23** were used.

More recently, Birman *et al.* extended the scope of their method to include β-lactams [124]. Surprisingly, however, little or no reaction took place when using BTM or its homobenzotetramizole analog HBTM as the chiral catalyst. Fortunately, the use of Cl-PIQ (**22**) under otherwise identical conditions (isobutyric anhydride, $CDCl_3$, room temperature) produced more promising results, affording the KR of (±)-4-phenyl-β-lactam with an *s* factor of 10 at room temperature. A survey of the solvent used in the reaction revealed that *tert*-amyl alcohol significantly increased both the selectivity and the reaction rate; however, due to limited solubility of the substrate, the overall concentration had to be lowered. The choice of the acid donor also proved critical as the use of less hindered analogues of isobutyric anhydride such as acetic and propionic anhydrides produced little to no enantioselection. Nonetheless, the reaction appeared to be general as various β-lactams could be resolved with high *s* factors ranging from *s* = 14 to 54, except perhaps for the *o*-chloro-substituted derivative, which displayed a rather disappointing selectivity (*s* = 3.1) and very low reaction rate (Scheme 41.48).

In 2009, Seidel *et al.* reported a particularly elegant dual catalytic approach to the KR of primary aryl alkyl amines [125]. Their strategy relied on the use of a chiral anion receptor such as a chiral thiourea, which could bind *in situ* to an achiral acyl pyridinium salt to form a chiral ion pair (Scheme 41.49).



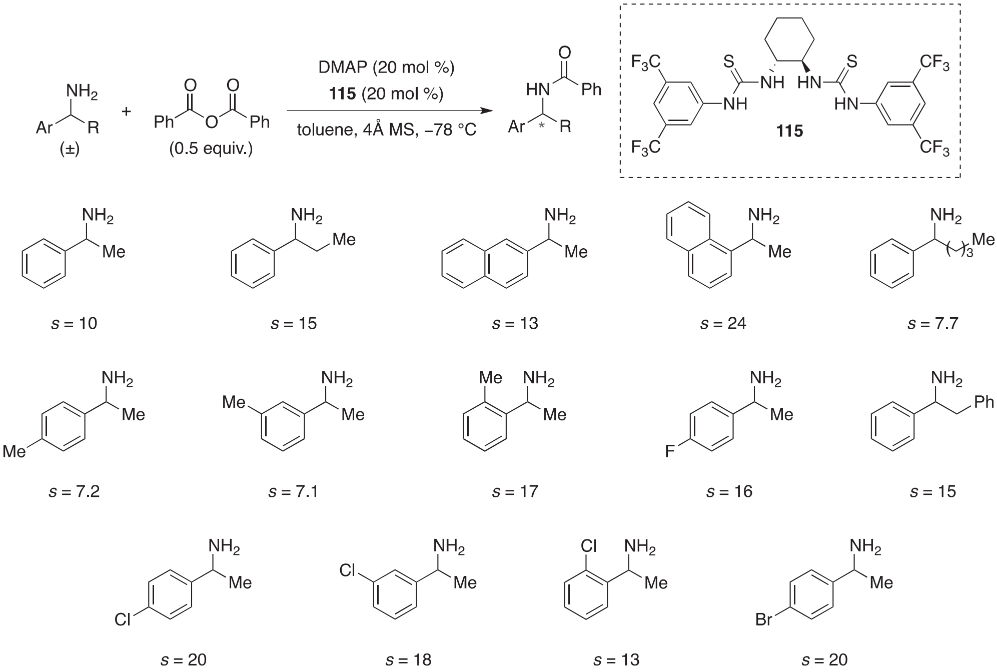
Scheme 41.48 Birman's amidine-based KR of β-lactams. [a] 4 equiv. of (i-PrCO)$_2$O were used.



Scheme 41.49 Proposed mechanism.

After screening various hydrogen bonding (HB) catalysts and testing various conditions (nature of the solvent, temperature, additives, catalyst loading, etc.) the best selectivities were obtained when performing the reaction using 20 mol% of chiral thiourea **115** in conjunction with 20 mol% of DMAP in toluene at −78 °C and using benzoic anhydride as the achiral acyl source. Under these conditions several primary aryl alkyl amines were resolved with good selectivities ranging from $s = 7.1$ to 24 (Scheme 41.50). Interestingly, substrates bearing an electron-withdrawing group gave higher selectivities regardless of its position on the aromatic ring, while bulkier groups on the alkyl chain did not impair the selectivity.

A more thorough investigation encompassing 22 nucleophilic species (**118–139**) and various HB catalysts (**115–117**) (Figure 41.13) with the idea of forming a more soluble chiral ion pair unveiled a new catalytic system that combined the readily available chiral thiourea-amide catalyst **116** with 4-di-*n*-propylaminopyridine (**120**) and led to improved selectivities at lower catalyst loadings [126].



Scheme 41.50 Seidel's dual catalysis-based KR of primary aryl alkyl amines.

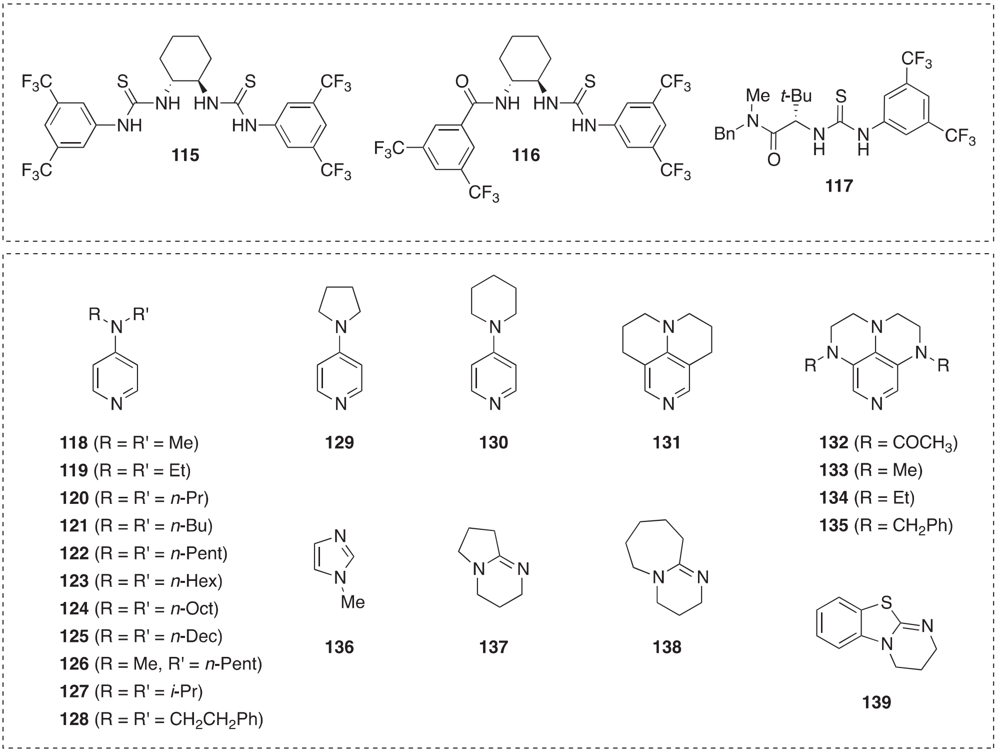
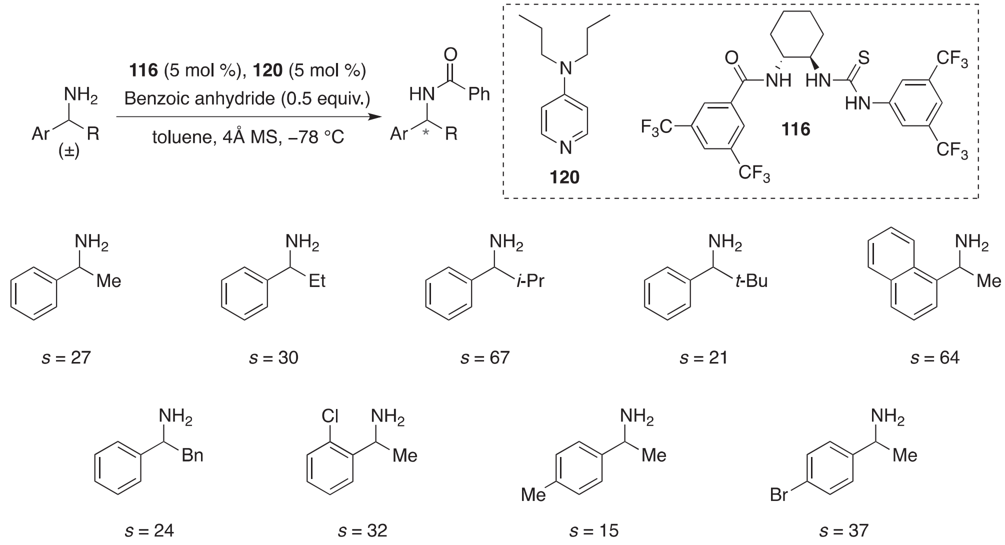


Figure 41.13 Evaluation of nucleophilic co-catalysts.

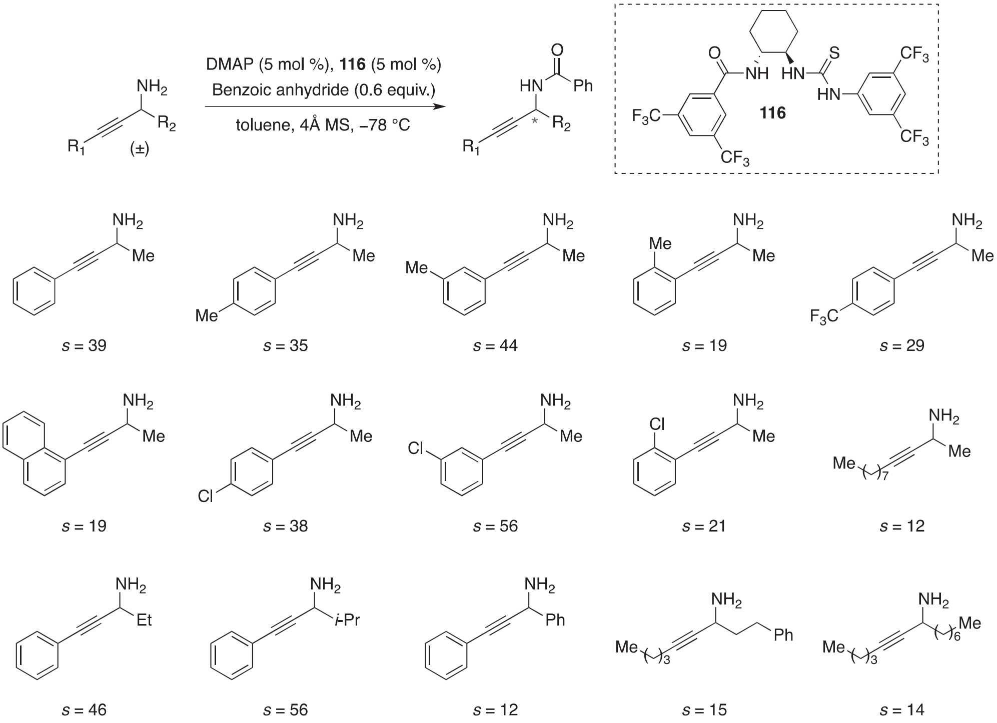
As outlined in Scheme 41.51, several primary aryl alkyl amines could thus be efficiently resolved by simply running the reactions in toluene at −78 °C using only 5 mol% of catalyst **120** in conjunction with 5 mol% of co-catalyst **116** and 0.5 equiv. of benzoic anhydride. Under these conditions, the corresponding benzamides were obtained with unprecedented levels of selectivity, ranging from *s* = 15 to 67.



Scheme 41.51 Scope of the KR of primary aryl alkyl amines using catalyst **120** in conjunction with co-catalyst **116.**

The same concept was also successfully applied to the KR of primary propargylic amines [127]. Hence, by combining catalyst **116** (5 mol%) with DMAP (**118**, 5 mol%) and by performing the reaction in toluene at −78 °C using benzoic anhydride as the achiral acyl source, several propargylic amines were resolved with good to excellent selectivities (Scheme 41.52). As a general trend, aryl-propargylic amines bearing substituents on different ring positions were readily accommodated, with substrates bearing a substituent in the *meta*-position giving rise to the highest selectivities independently of the electronic nature of the substituent. Additionally, propargylic amines with two aliphatic residues were also viable substrates, affording the corresponding benzamides with *s* factors of between 12 and 15. Finally, this catalytic system could also be used to distinguish between two different π-systems, as exemplified by the effective resolution of the α-phenyl propargyl amine derivative (*s* = 12).

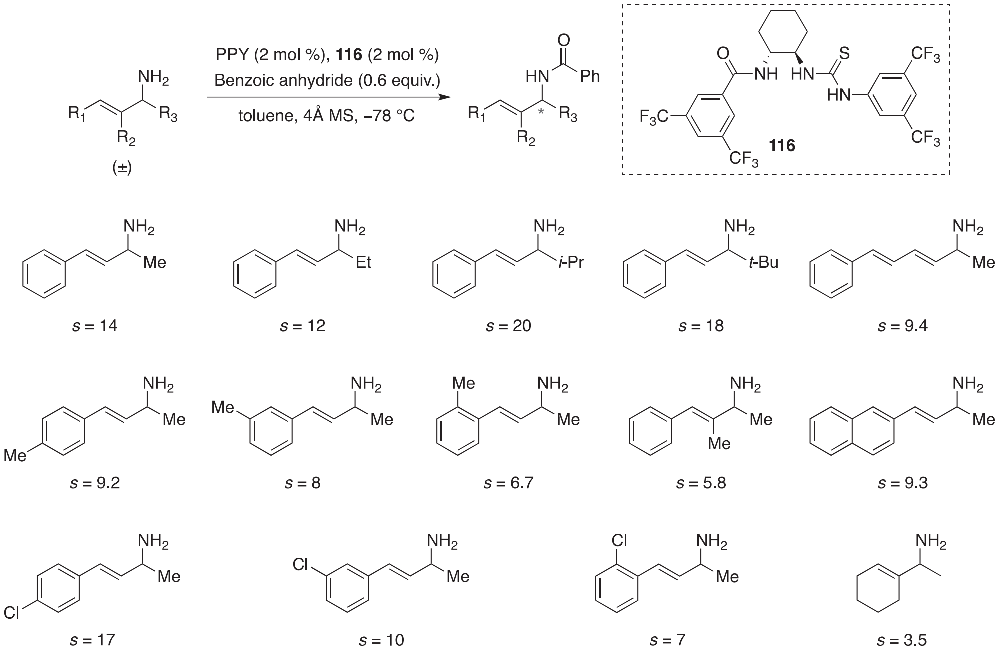
Allylic amines also proved to be suitable substrates for the dual catalysis/anion-binding approach developed by Seidel *et al.*; however, the selectivities were slightly lower than that obtained with either primary aryl alkyl amines or propargylic amines [128]. This decrease in selectivity was attributed to the higher nucleophilic-



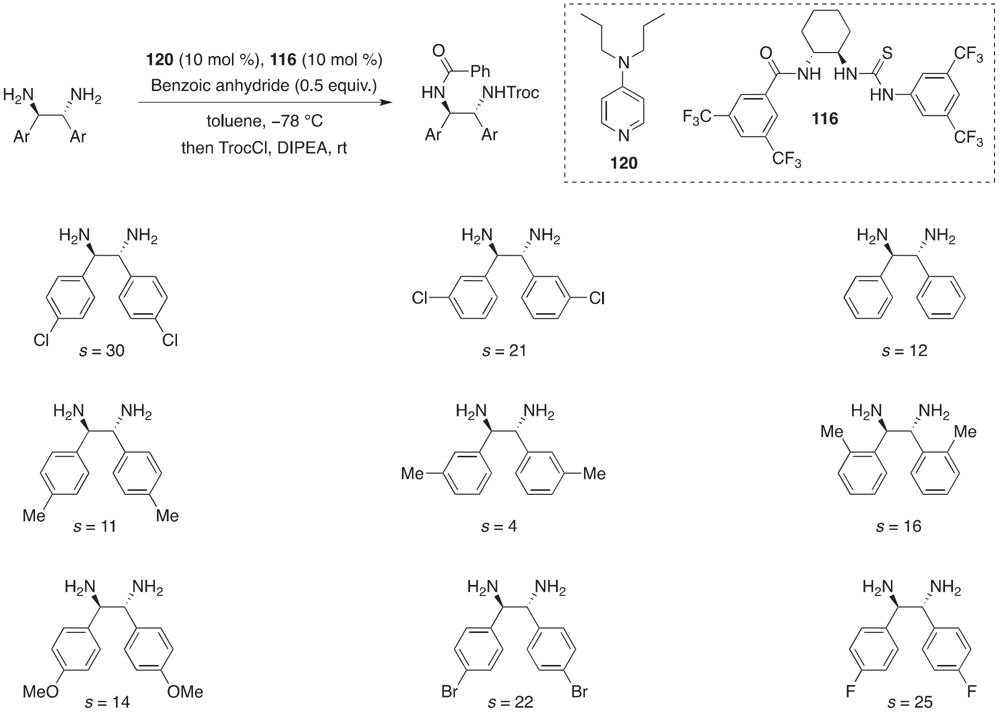
Scheme 41.52 Seidel's dual catalysis-based KR of propargylamines.

ity of allylic amines compared to that of other primary amines and therefore imposed a fine-tuning of both the nucleophilic catalyst and the achiral acyl donor. As a general trend, the best selectivities were obtained when using the more nucleophilic 4-PPY (**129**) as the co-catalyst instead of DMAP in combination with the less reactive benzoic anhydride while performing the reaction in toluene at −78 °C. Under these conditions, various primary allylic amines were resolved with moderate to good selectivities ranging from *s* = 3.5 to 20 (Scheme 41.53). Hence, whereas an exchange of the methyl group (*s* = 14) with an ethyl group (*s* = 12) in the parent substrate led to a slight decrease in selectivity, substrates bearing a bulkier group such as an isopropyl or *tert*-butyl were resolved with higher selectivities (*s* up to 20). Introduction of an electron-donating substituent such as a methyl group in any of the positions on the phenyl ring led to lower s factors (6.7 < *s* < 9.2) while electron-withdrawing groups such as a chloro substituent in the *para*-position had a positive effect on the efficiency of the resolution (*s* = 17), while the same substituent in the *meta* (*s* = 10) or *ortho* (*s* = 7) position led to a drop in selectivity.

Eventually, the use of a catalytic amount of chiral amide-thiourea anion-receptor **116** in conjunction of with achiral nucleophilic co-catalyst **120** allowed for the resolution of several 1,2-diaryl-1,2-diaminoethanes (Scheme 41.54) with useful levels



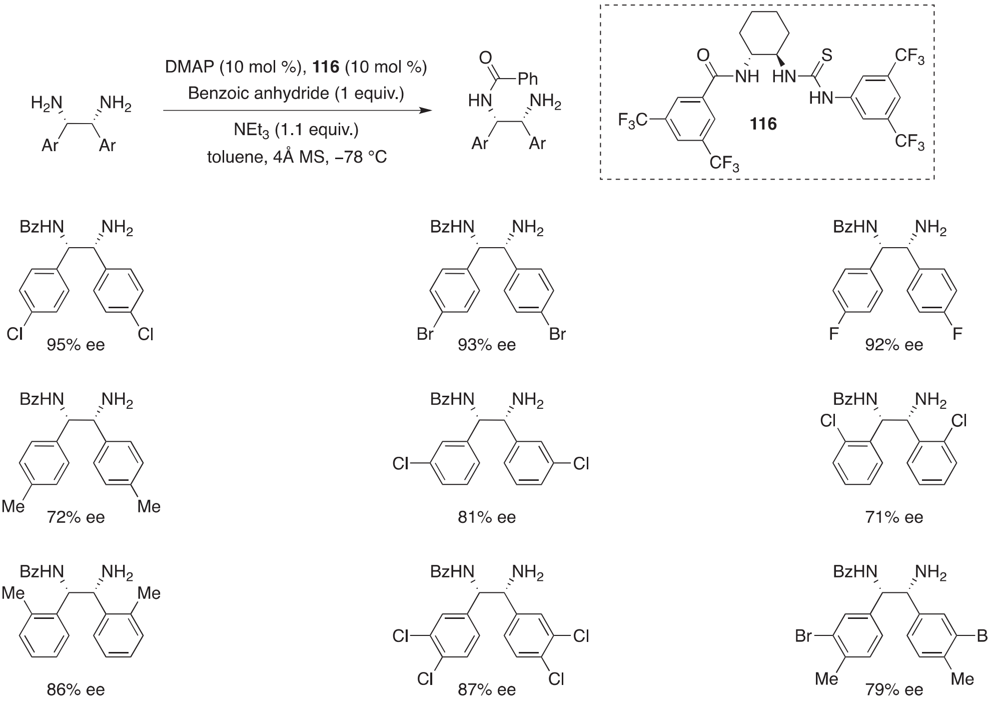
Scheme 41.53 Seidel's dual catalysis-based KR of allylamines.



Scheme 41.54 Seidel's dual catalysis-based KR of 1,2-diaryl-1,2-diaminoethanes. (DIPEA = diisopropylethylamine).

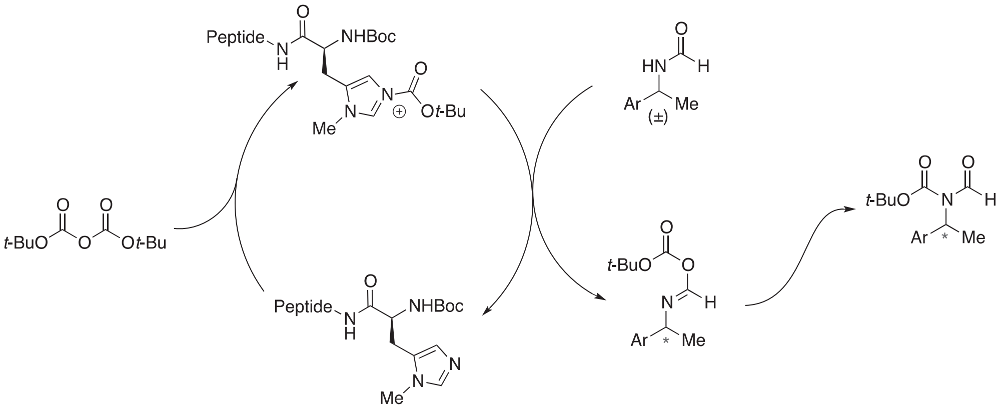
of selectivity (*s* factors up to 30) [129]. As a general trend, electron-poor diamines led to higher selectivities than the more electron-rich ones, which is most likely due to the increased reactivity of the latter.

After developing efficient conditions for the KR of benzylic-, propargylic-, allylic amines, and more recently C_2-symmetric diamines, Seidel *et al.* set out to implement their method to the desymmetrization of *meso*-diamines [130]. In retrospect, this was not an easy task due to the inherently high nucleophilicity of diamines and the fact that they are prone to bis-acylation. Luckily, however, after screening various catalytic systems, the ones used for the KR of propargylic amines (catalyst **116** [10 mol%], DMAP [10 mol%]) appeared to be compatible, affording the desired mono-benzoylated products with excellent enantioselectivities (ee up to 95%) and high yields (up to 82%) as long as triethylamine was added to the reaction mixture (Scheme 41.55).



Scheme 41.55 Seidel's dual catalysis-based desymmetrization of *meso*-diamines.

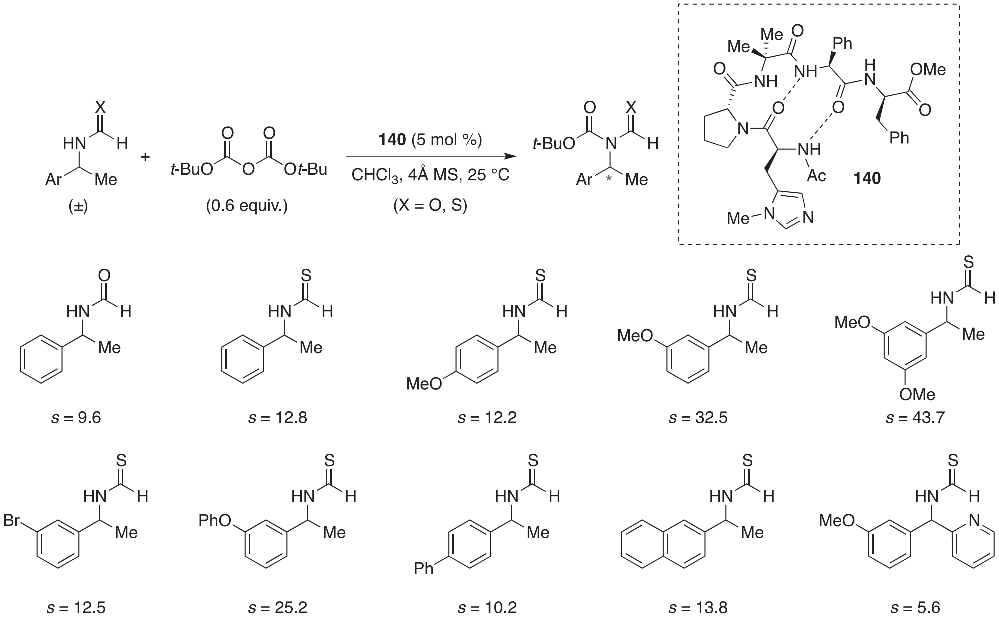
In 2010, Miller and coworkers introduced a new catalytic system for the KR of amines based on a simple π-methylated histidine scaffold [131]. Their strategy relied on the idea that simple formamides would react through a kinetically favored *O*-acylation followed by a rearrangement of the resulting unstable *O*-acylated intermediate to the more stable imide (Scheme 41.56).



Scheme 41.56 Miller's strategy for the KR of amines.

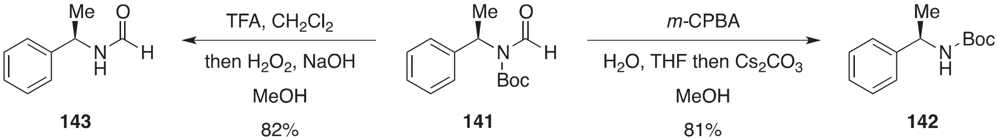
Hence, by using pentapeptide **140** (5 mol%) in conjunction with Boc$_2$O (0.6 equiv.), Miller and coworkers were able to resolve various formamides and thioformamides with high selectivities (*s* up to 43.7, Scheme 41.57). Interestingly, thioamides were more readily acylated and with higher selectivities than amides.

The possibility of selectively removing either one of the *N*-protecting groups under mild conditions is another interesting feature of this method. Hence, **141** could be exclusively converted into either carbamate **142** or formamide **143** via an



Scheme 41.57 Miller's peptide-based KR of formamides and thioformamides.

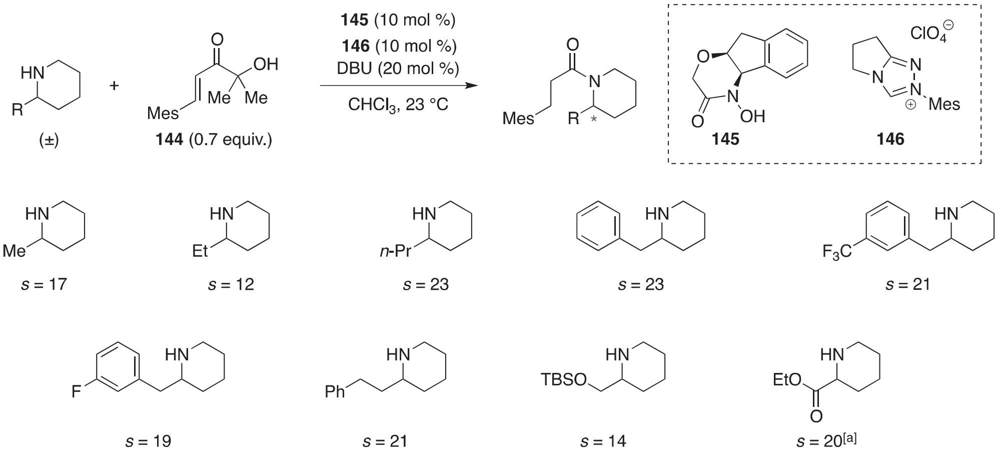
oxidative hydrolysis or an acidic cleavage of the Boc group and S-to-O exchange, respectively (Scheme 41.58).



Scheme 41.58 Miller's peptide-based KR of formamides and thioformamides (TFA = trifluoroacetic acid).

In 2011, Bode *et al.* reported a unique dual-catalysis redox approach to the KR of secondary amines based on the catalytic generation of an acyl azolium species [132]. Indeed, these species, which can undergo rapid acyl transfer in the presence of various nucleophiles such as water, alcohols, or thiols, are absolutely inert in the presence of amines except if an additive such as imidazole or 1-hydroxy-7-azabenzotriazole (HOAt) is added to the reaction mixture [133].

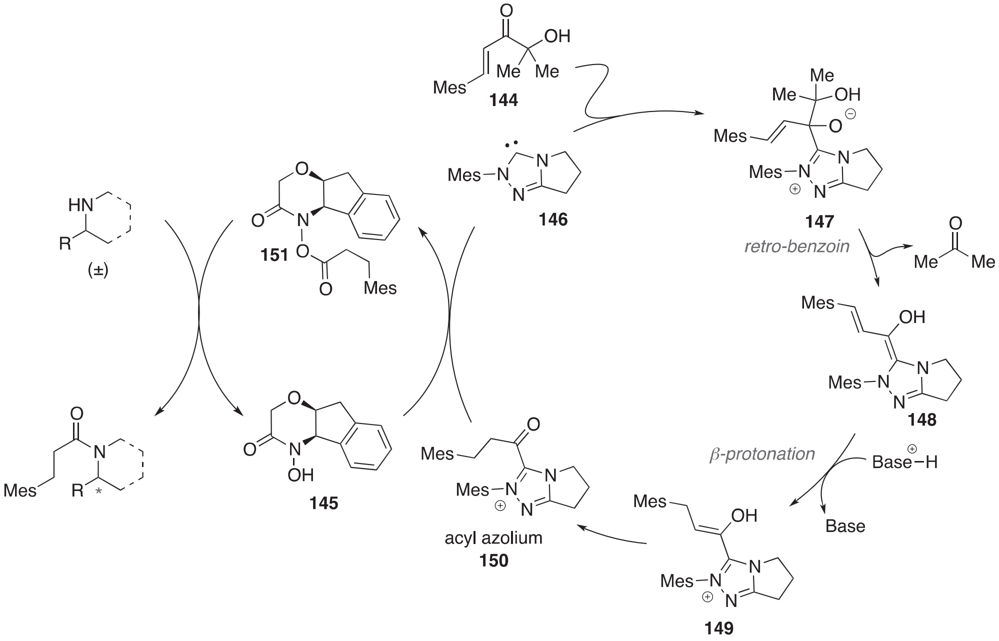
Various chiral imidazoles and triazoles were therefore tested in the KR of 2-methylpiperidine; however, little or no enantioselectivity was observed. Fortunately, after screening various co-catalysts, chiral hydroxamic acids [134], in particular the *cis*-(1*R*,2*S*)-aminoindanol-derived hydroxamic acid **145**, were found to give excellent results at room temperature. Finally, further optimization of the catalytic resolution conditions, including the use of mesityl-substituted α-hydroxyenone **144** to deter N-heterocyclic carbene (NHC)-catalyzed side reactions [135], led to the effective KR of various 2-substituted piperidines with selectivity factors ranging from *s* = 12 to 23 (Scheme 41.59).



[a] 1 equiv. of ketone **144** was used.

Scheme 41.59 Bode's N-heterocyclic carbene-based KR of 2-substituted piperidines.

By monitoring the reaction through 1H NMR spectroscopy, Bode *et al.* were eventually able to show that the acylated intermediate **151** was the active acylating species (Scheme 41.60). This was later confirmed after independently preparing it and employing it as a stoichiometric reagent ($s = 18$).

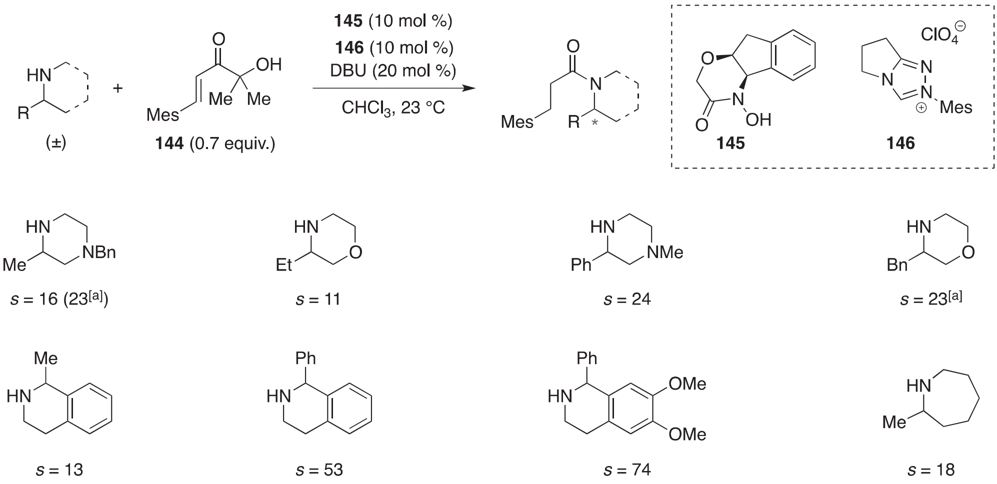


Scheme 41.60 Proposed synergistic catalytic cycles for the KR of amines.

Various other classes of cyclic amines were also evaluated. Hence, substituted piperazines and morpholines, both of which are components of chiral pharmaceuticals, were resolved with *s* factors ranging from *s* = 11 to 24, while tetrahydroisoquinolines were resolved with excellent *s* factors, ranging 53 to 74 (Scheme 41.61).

Following these initial results, Bode *et al.* were able to improve the reaction conditions to reach higher levels of selectivity on a broader range of substrates [136]. Hence, *i*-PrOAc appeared to be a suitable alternative to CH_2Cl_2, while K_2CO_3 could be used in the place of DBU to simplify the reaction workup without altering the selectivity. Finally, the use of the Br-substituted catalyst **152** offered improved reactivity, thus allowing the catalyst loading to be reduced down to 5 mol%.

These new reaction conditions afforded improved selectivities on all the substrates previously tested such as piperidines, morpholines, tetrahydroisoquinolines, and azepanes, but also allowed the resolution of several valuable amines that

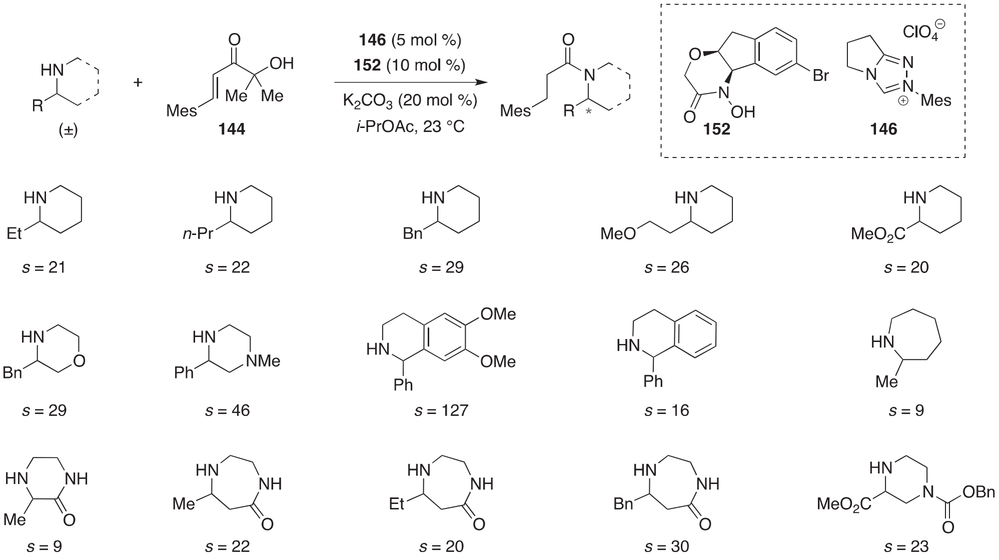


[a] 1 equiv. of ketone **144** was used.

Scheme 41.61 Bode's N-heterocyclic carbene-based KR of piperazines, morpholines, tetrahydroisoquinolines, and azepanes.

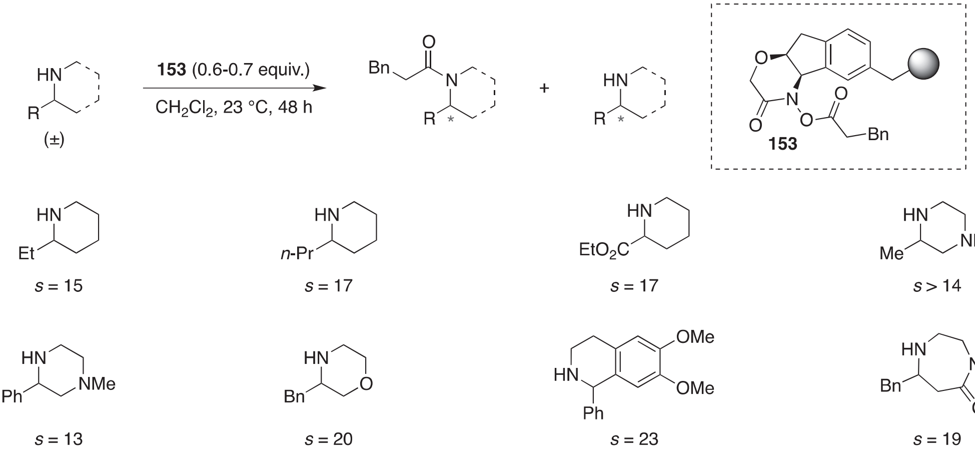
were unreactive or not effectively resolved with the original procedure, such as 3-alkyl-piperazinones, 7-substituted 1,4-diazepanones, and piperazines bearing *N*-carbamate protecting groups (Scheme 41.62).

Most recently, Bode and coworkers developed a particularly robust and recyclable polymer-bound reagent [137] for the room temperature KR of secondary



Scheme 41.62 Bode's N-heterocyclic carbene-based KR of piperidines, piperazines, morpholines, isoquinolines, and azepanes, as well as substrates containing a lactam or a carbamate functional group.

amines (Scheme 41.63). In addition to delivering high selectivities, this supported reagent has the advantage of transferring more easily-removable acyl groups than has previously been possible using the soluble catalysts.



Scheme 41.63 Bode's supported reagent for the KR of nitrogen heterocycles.

41.4
Concluding Remarks

It is apparent from the preceding survey that the KR alcohols and amines and the ASD of *meso*-diols by nucleophilic catalysis has now emerged as a very powerful approach to the preparation of enantiomerically highly enriched derivatives. Moreover, although the vast majority of development work has been carried out for acyl group transfer to give ester and amide or carbamate products from alcohols and amine substrates, respectively, there is a substantial emerging body of work relating to the transfer of other groups. Given the ubiquity of phosphate-containing groups in many molecules of importance in biological signaling cascades, and the notoriously lengthy synthetic sequences by which enantiomerically enriched, for example, phosphorylated inositol derivatives are classically prepared, enantioselective phosphoryl transfer processes as pioneered by Miller *et al.* hold immense promise for the preparation of probes for interrogating signal transduction pathways of medicinal importance. Similarly, given the widespread use of silyl ethers as protecting groups in complex syntheses, the development of enantioselective silyl transfer processes offers tremendous prospects for enabling efficient access to key synthetic precursors for numerous synthetic applications. Although the enantioselective transfer of sulfonyl groups is in comparative infancy, this type of group transfer has significant promise for the efficient preparation of enantiomerically enriched sulfonate esters from alcohols, for use as precursors for elimination and substitution reactions, and also for the as yet unreported preparation of enantiomerically enriched sulfonamides from amines. Inevitably, great strides will be made in all these directions and the insights gained from the study of all these different classes of substrates and transfer reagents will cross-fertilize to enable a deeper and more synoptic understanding of the mechanisms involved in these selective catalytic procedures. We hope that the overview provided herein will aid this evolution and encourage future innovation in this exciting area.

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42
Three or More Components Reactions (Single Catalyst Systems)

René Tannert, Antonio Moran, and Paolo Melchiorre

42.1
General Introduction

Multicomponent reactions (MCRs) are processes in which three or more reactants, which can co-exist in the same reaction mixture, are combined to access complex products by means of two (or more) bond-forming events and in a single synthetic step [1]. This chapter mainly focuses on asymmetric MCRs that fall in the wider definition of domino reactions [2]. According to the definition by Lutz Tietze [3], domino processes are sequences of chemical transformations that take place under the same reaction conditions. Thus, all the reagents and catalysts are added at (or nearly at) the outset of the process to undergo a chemical transformation whose product becomes the substrate for the next step, whose product again becomes the substrate for the next step, and so on, until a product stable to the reaction conditions is reached. MCRs pose an intellectually stimulating yet challenging problem to synthetic chemists. They require careful consideration of the compatibility of the transiently formed intermediates and the substrates, which should not undergo alternative irreversible reactions to form by-products. Thus, achieving a high degree of chemoselectivity is the greatest obstacle in the design of MCRs [4]. But success results in a big payoff. MCRs reduce time-consuming and costly protection/deprotection and isolation procedures of intermediates. They are also optimal atom-economical processes, since all (or many) of the atoms in the reactants end up in the desired product [5]. They are, therefore, a way to achieve green chemistry and develop economical processes for manufacturing pharmaceuticals and other fine chemicals [5c]. In addition, this experimentally simple synthetic strategy offers the potential for rapidly increasing structural and stereochemical complexity. In a single synthetic step, it converts simple starting materials into complex molecular systems containing multiple stereocenters. Even more appealing is the development of asymmetric catalytic MCRs [6]. By combining multiple asymmetric, catalytic transformations in a domino sequence chemists can impart increased enantiomeric excess to the final product when compared to the corresponding discrete transformations. This requires a chiral catalyst that can effectively drive, in a stereocontrolled fashion, consecutive catalytic reactions. The

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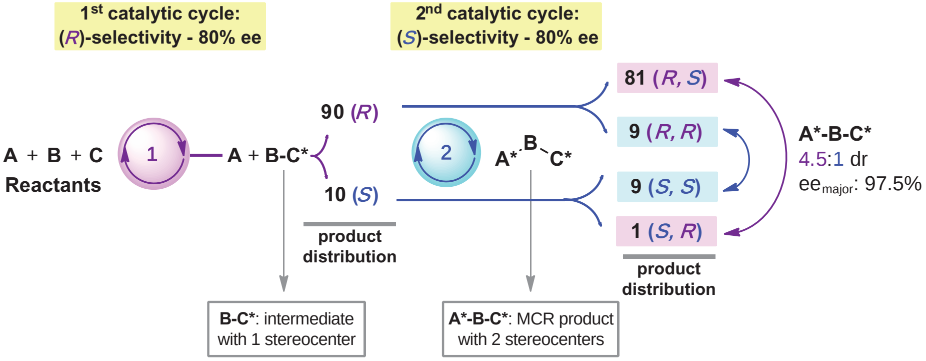


Figure 42.1 Schematic explanation of the Horeau principle and the product enantioenrichment within catalytic asymmetric MCRs. A three-component reaction in which the chiral catalyst promotes two consecutive bond-forming events is considered; it is assumed that both catalytic steps confer a 9 : 1 enantiomeric ratio (80% ee).

Horeau principle provides the mathematical foundation for rationalizing the enantioenrichment observed along successive catalytic cycles of asymmetric MCRs [7]. The simple calculations shown in Figure 42.1 reveal that this strategy can provide the major diastereomer of a chiral product that has two stereogenic centers with exquisite levels of enantiocontrol. This is despite combining two consecutive catalytic processes that might be only moderately selective (e.g., 80% ee + 80% ee = 97.5% ee).

Given the above, it is easy to understand why the many synthetic benefits of MCRs have attracted the interest of asymmetric organocatalysis researchers. The stability, versatility, and compatibility with distinct functional groups make simple chiral organic catalysts perfectly suited for engineering effective asymmetric catalytic methods. The marriage with asymmetric organocatalysis has been a further step in consolidating MCRs as a powerful and reliable strategy for the stereoselective one-step synthesis of complex molecules [8]. The synthetic potential of this approach has been validated by recent applications of asymmetric organocatalytic domino reactions to the total synthesis of natural products [9].

Instead of providing an exhaustive list of organocatalytic asymmetric MCRs, we seek here to critically describe the developments achieved in the field, charting the ideas, conceptual advances, and milestone reactions that have been essential for reaching the present, highly practical levels of synthetic efficiency. We show how, following the early, conceptually simple asymmetric MCRs, a deeper understanding of the organocatalytic reactivity principles has led to the engineering of more sophisticated substrate combinations. Nowadays, awareness of the synthetic power of organocatalytic MCRs has prompted organic chemists to revisit and redefine the potential of many multicomponent transformations, which were conceived in a previous chemical era. The Strecker reaction (1850), the Hantzsch dihydropyridine synthesis (1882), the Biginelli dihydropyrimidine synthesis (1891), the Mannich reaction (1912), and Ugi four-component reactions (Ugi-4CRs) (1959) have all been rendered catalytic and enantioselective (Section 42.3).

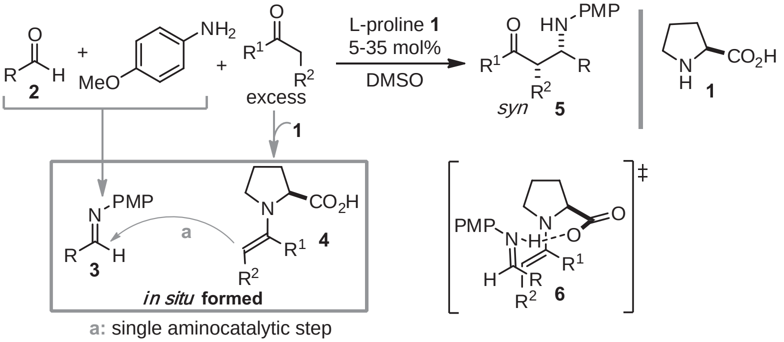
The chapter discusses two distinct modes of organocatalytic activation that are operative in the MCRs. Small-molecule organic catalysts can exert their catalysis functions by following two completely different activation patterns [10]. They can exploit *covalent*-based modes of activation [10b], effectively condensing with a substrate (generally a carbonyl compound) to form a covalently bonded reactive catalytic species. Alternatively, they can use *non-covalent* approaches [10c], based on the cooperation of multiple weak attractive interactions between the catalyst and the substrates. We have covered asymmetric organocatalytic MCRs in which at least three different reagents are mixed together at the outset of the process in the presence of a single organocatalyst, or where addition of the last component occurs sequentially in a reasonable timeframe (not more than 1 h after the reaction was started) to claim all reagents as coexisting in the reaction mixture [11]. Thus we have not covered many of the effective two-component domino reactions and approaches based on the synergistic actions of distinct (organo)catalytic systems. In addition, the definition of a multicomponent domino process would discount any example in which the reaction conditions are altered during the process, the result of which is that some useful reactions have not been discussed. We have decided to briefly detail a recent strategy, involving uninterrupted sequences of one-pot organocatalytic reactions, used to streamline the preparation of active pharmaceutical ingredients, since this approach nicely testifies to the synthetic power of organocatalytic MCRs (Section 42.2.4).

42.2
Covalent Modes of Catalysis – Developing MCRs by Asymmetric Aminocatalysis

Catalysis by chiral primary and secondary amines is known as “asymmetric aminocatalysis” [12]. This strategy has been central to organocatalysis since its inception. Aminocatalysis, which exploits fundamental and well-established mechanistic patterns, mainly using the chemistry of simple enamine [13] and iminium ion intermediates [14], has greatly expanded the chemist’s ability to asymmetrically functionalize carbonyl compounds. More generally, achievements in this field led to a renaissance in the area of catalysis mediated by small organic chiral molecules. This happened with asymmetric MCRs too. Chiral amines were quickly recognized as ideal for catalyzing highly efficient domino processes. This is mainly because of the ability of a single chiral amine to integrate orthogonal activation modes of carbonyl compounds (enamine and iminium ion catalysis) into more elaborate reaction sequences [8]. The synthetic limitation is that aminocatalytic MCRs require the presence of at least one carbonyl compound.

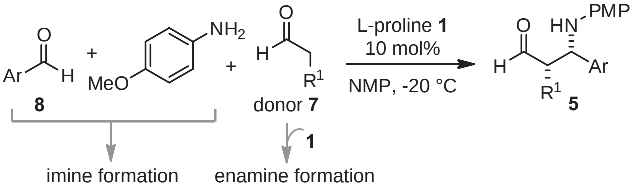
42.2.1
Asymmetric MCRs Based on a Single Aminocatalytic Step

Since the beginning of the last decade, chiral secondary amines have been used to design asymmetric MCRs. Initial strategies were based on three-component processes where only a single step was under the control of the chiral aminocatalyst. These early examples did not construct sophisticated catalytic machineries. However, they established the synthetic power of merging domino reactions with asymmetric aminocatalysis to rapidly access useful chiral building blocks from simple starting materials. In 2000, Benjamin List, following studies on the proline-catalyzed intermolecular asymmetric aldolization [13], extended the enamine catalytic concept to the Mannich reaction [15], one of the most powerful and venerable organic transformations for the construction of chiral nitrogen-containing molecules [16]. The direct three-component Mannich reaction between an aldehyde, *p*-anisidine, and a ketone catalyzed by proline **1**, without prior enolate or imine formation, provided the first example of an organocatalytic asymmetric MCR (Scheme 42.1).



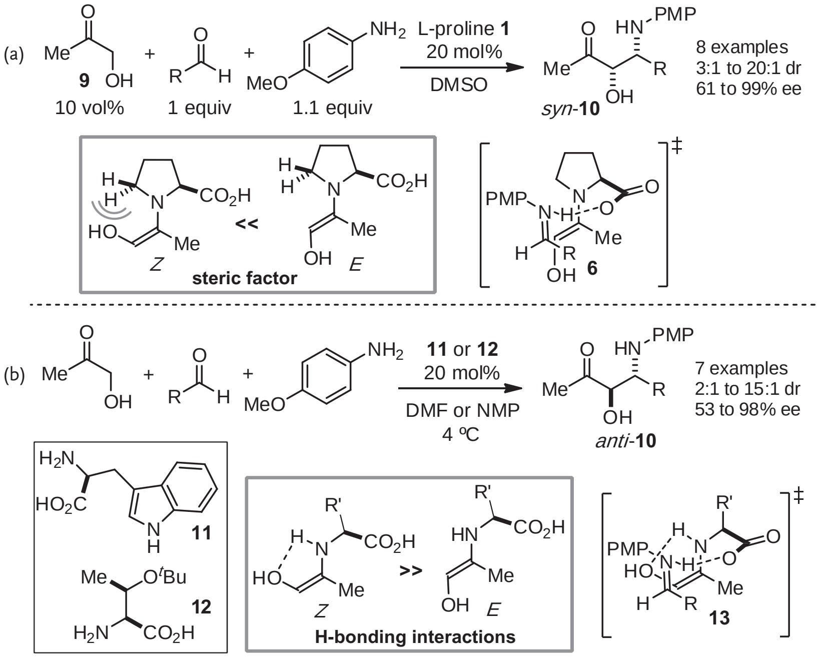
Scheme 42.1 Proline-catalyzed asymmetric three-component Mannich reaction: enamine-catalyzed enantio-determining step (PMP = *p*-methoxyphenyl).

The chemistry exploits the mild condition of proline catalysis, which does not interfere with the *in situ* generation of the imine **3** by spontaneous condensation of *p*-anisidine and aldehyde **2**, while promoting the formation of the nucleophilic enamine intermediate **4** by selective catalyst condensation with the keto-substrate. A highly structured transition state of type **6** [17], in which both the amino moiety and the carboxylic group of the proline scaffold execute crucial catalytic functions, secures the formation of the Mannich adducts **5** with high enantioselectivity and *syn*-diastereoselectivity. The most notable feature of the multicomponent Mannich reaction was the ability of proline **1** to catalyze the transformation in a highly chemoselective fashion, minimizing the competing aldol process (direct enamine attack to the aldehyde **2**): indeed, the aldol derivatives were detected in a low amount. Extending this MCR system to include aliphatic aldehydes as the pronucleophile was a tougher test of the ability of proline **1** to impart chemoselectivity [18]. The two aldehydes had to be selectively partitioned into discrete components of the reaction, the nucleophilic enamine donor and the electrophilic imine. This was addressed by using an aliphatic and an aromatic aldehyde, **7** and **8**, respectively (Scheme 42.2). The reaction temperature had to be strictly maintained at –20 °C to avoid the competing self-aldolization of the enolizable aldehyde **7** [19]. This approach provided an early example of how, by carefully considering the intimate reactivity of the catalytic intermediates of aminocatalysis, researchers could move toward engineering challenging substrate combinations.



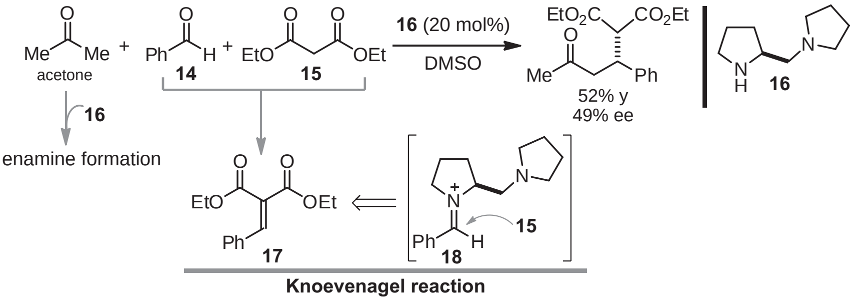
Scheme 42.2 Three-component Mannich reaction of aldehydes; NMP = *N*-methyl-2-pyrrolidinone.

The power of proline to catalyze the Mannich MCR imparting *syn* diastereoselectivity was also used to directly synthesize *syn*-1,2-amino alcohols **10** [15b]. The use of α-hydroxy acetone **9** resulted in complete regioselectivity for the hydroxy-substituted alkyl chain, and allowed the highly stereoselective preparation of valuable building blocks (Scheme 42.3a). In 2007, Barbas and coworkers implemented an *anti*-selective multicomponent Mannich reaction of hydroxy ketones, thus complementing the ability of proline catalysis to afford only *syn*-1,2-amino alcohols **10** (Scheme 42.3b) [20]. Chiral primary amines, such as L-tryptophan **11** and O-*t*-butyl L-threonine **12**, were key for controlling the stereochemical outcome of the Mannich MCR. Similarly to proline catalysis, these amino acids induce the formation of a transition state **13** in which a specific hydrogen-bonding interaction directs the imine approach from the upper face of the enamine (hydrogen-bonding-directed catalysis). The diastereo-divergent pathways arise from the opposite configuration of the reactive enamine intermediate. For steric reasons, proline favors the formation of an (*E*)-configured species (see transition state **6**). Primary amines, however, enable the selective formation of a (*Z*)-configured enamine (as shown in **13**). This is due to non-covalent attractive interactions between the hydroxyl group and the catalyst N–H group, which acts as a linchpin for transition state organization.



Scheme 42.3 MC Mannich reaction for individual access to (a) *syn* and (b) *anti*-amino alcohols **10**.

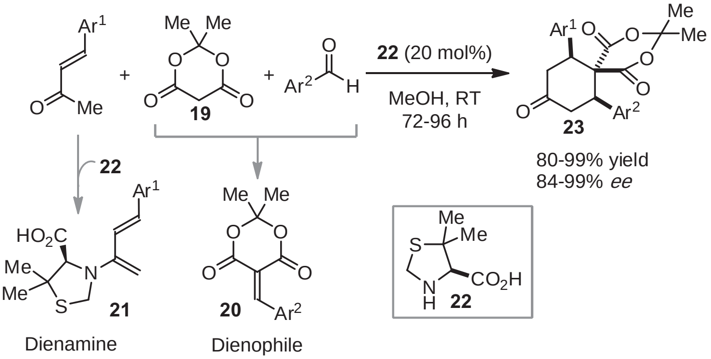
Enamine catalysis provided the synthetic platform for a second example of asymmetric MCR. In 2001, Barbas and colleagues described a Knoevenagel/Michael reaction sequence between acetone, benzaldehyde (**14**), and diethyl malonate (**15**) catalyzed by the chiral secondary amine **16** (Scheme 42.4). Despite the moderate level of enantioselectivity, this reaction was engineered upon rather sophisticated catalytic machinery [21]. The catalyst promoted both individual steps of the MCR, although only the second enamine-catalyzed process was stereo-determining. The



Scheme 42.4 Three-component Knoevenagel/Michael reaction: both steps are catalyzed by the amine **16;** only the second enamine path is stereo-determining.

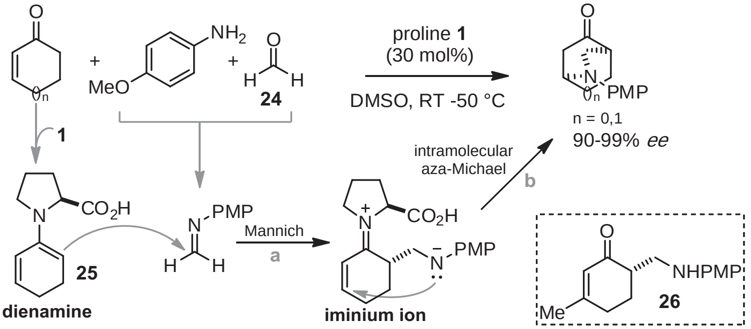
amine **16** is presumably involved in the formation of the iminium ion intermediate **18**, which is the key species in the Knoevenagel condensation. The nucleophilic attack of malonate **15** followed by dehydration led to the *in situ* generation of the actual electrophilic Michael acceptor **17**.

The Knoevenagel reaction is a venerable transformation, which provided the foundations for the development of modern aminocatalysis more than a century ago [12a]. Interestingly, it is now recognized as a useful transformation for multicomponent organocatalytic reactions. It was used to extend the applicability of organocatalytic MCR to other classes of carbonyl compounds, such as enones. In 2003, Barbas and coworkers started an interesting series of investigations on the coupling of three distinct reagents through sequential Knoevenagel and Diels–Alder reactions [22]. One example of the efficiency and broad scope of their approach is summarized in Scheme 42.5 [22a]. In the initial Knoevenagel reaction, the aldehyde reacts with Meldrum acid (**19**) to form the reactive dienophile **20**. In the second step, the secondary aminocatalyst 5,5-dimethylthiazolidinium-4-carboxylate (**22**) easily condenses with the enone, leading to the transient formation of dienamine intermediate **21**. This covalent species can readily participate in Diels–Alder processes by acting as activated chiral dienes, thus intercepting the electron-deficient dienophile **20**. The chemistry allows the construction of spiro-compounds **23** in a rapid and effective way. The strategy was extended to a four-component reaction, including the *in situ* generation of the enone substrate by a Wittig reaction between a second aldehydic substrate and a phosphorane [22b]. Implementing this strategy, however, required addition of the reagents in a sequential, temporarily well-defined order.



Scheme 42.5 Asymmetric Knoevenagel/Diels–Alder reaction.

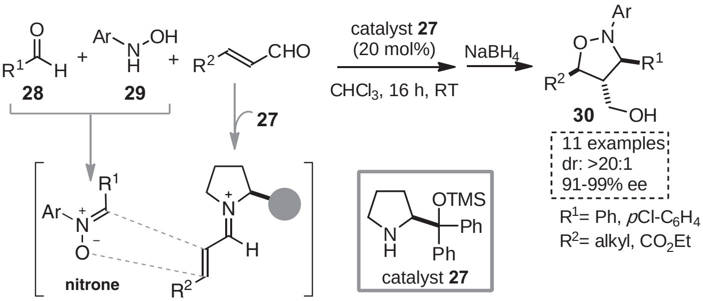
Conceptually, these studies demonstrated that effective asymmetric MCRs could be designed using aminocatalytic intermediates (dienamine **21**) and reactivities (pericyclic patterns) other than an enamine and the nucleophilic addition manifold. A similar domino sequence served for the development of a formal direct aza-Diels–Alder reaction between cyclic enones and imines, generated *in situ* by spontaneous condensation of *para*-anisidine and formaldehyde (**24**) (Scheme 42.6) [23]. In analogy with the example depicted in Scheme 42.5, the chemistry exploited the ability of the proline catalyst **1** to condense with enones while inducing the formation of the covalent dienamine of type **25** (notice the structural and electronic similarity with intermediate **21** in Scheme 42.5), contributing a potential diene for a pericyclic process. Experimental observations, however, supported a different mechanism of catalysis. The exclusive formation of the Mannich adduct **26** when using a hindered β-methyl cyclohexenone, and the stereochemical outcome of the process, as inferred by X-ray crystallographic analysis, pointed to a stepwise Mannich/cyclization domino reaction under a well-defined enamine–iminium ion activation sequence.



Scheme 42.6 A Mannich/aza-Michael tandem reaction under an enamine/iminium ion activation sequence.

This study provided one of the first demonstrations [24] that chiral secondary amines can integrate orthogonal activation modes of carbonyl compounds (enamine and iminium ion catalysis) into more elaborate reaction sequences, catalyzing more than one stereocontrolled bond-forming event. As detailed in Section 42.2.2, this concept greatly permeated and boosted future developments in the field of asymmetric organocatalytic MCRs.

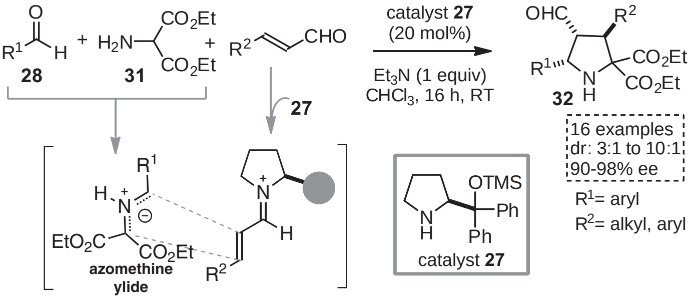
Successively, iminium ion activation was also used as a reactivity platform for developing asymmetric MCRs. In 2007, Córdova and colleagues began a series of investigations on 1,3-dipolar cycloadditions based on the *in situ* formation of the 1,3-dipole, while the transient iminium ion intermediate, generated by catalyst condensation with α,β-unsaturated aldehydes, provided the required chiral C–C dipolarophile [25, 26]. The chemistry secured direct access to useful five-membered heterocycles. As depicted in Scheme 42.7, the combination of *N*-arylhydroxylamines **29** and aromatic aldehydes **28** led to *in situ* generation of the resulting nitrone. The cycloaddition pathway, driven by the chiral secondary amine catalyst **27**, afforded synthetically valuable isoxazolidines **30** with very high stereocontrol [25]. Notably, to address the multiple chemoselectivity issues intrinsically connected



Scheme 42.7 Three-component 1,3-dipolar cycloaddition: iminium ion-catalyzed enantiodetermining step. Protocol point: **28** and **29** were premixed for 1 h. The shaded circle represents the catalyst scaffold.

with this MCR (i.e., the condensation of *N*-arylhydroxylamines with the enal substrate), components **28** and **29** had to be premixed for 1 h, to ensure selective formation of the nitrone intermediate, before addition of the catalyst and the enal. The catalyst of this three-component reaction, the diphenylprolinol silyl ether **27**, is one of the more versatile and commonly used chiral secondary amines. This is because it allows the highly stereoselective functionalization of aldehydes by exploiting different aminocatalytic activation modes [27]. Its use has led to many other MCRs being performed with great efficiency. We discuss these findings in more detail in the following sections.

A similar strategy has been used to directly synthesize functionalized pyrrolidines **32** (Scheme 42.8) [26]. In this case, the 1,3-dipolar cycloaddition required *in situ* formation of an azomethine ylide by condensation of 2-aminomalonate **31** and aldehydes **28**. Again, the iminium ion intermediate, generated from enals and catalyst **27**, served as the chiral dipolarophile to enforce a high level of stereocontrol.

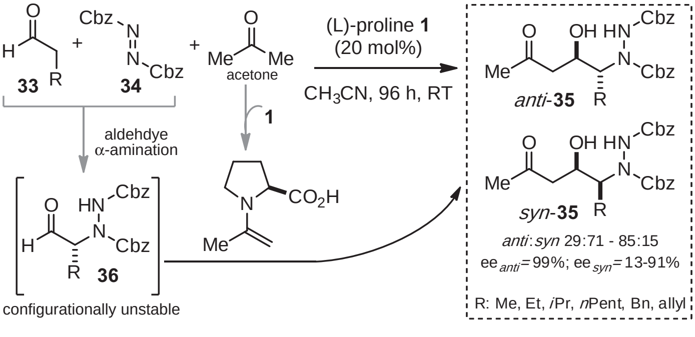


Scheme 42.8 Three-component 1,3-dipolar cycloaddition: iminium ion-catalyzed enantiodetermining step. Protocol point: **28** and **31** premixed for 1 h. The shaded circle represents the catalyst scaffold.

42.2.2
Asymmetric MCRs Based on Two Aminocatalytic Steps

A fundamental step toward more effective aminocatalytic domino processes was the ability to integrate mechanistically distinct modes of catalysis (iminium and/or enamine activation) [28] in a single sequence, with the aim of securing direct access to complex products from simple starting materials. Scheme 42.6 above shows an initial example. Although elegant, this approach required careful design of the substrates. This is because the first step of the multicomponent reaction must generate a multifunctional intermediate able to successively undergo an intramolecular process. This prerequisite somewhat limits the strategy's applicability. Combining two *intermolecular* and stereoselective bond-forming events would provide a more versatile and powerful strategy for rapidly assembling complex chiral molecules.

In 2003, a proline-catalyzed enamine–enamine activation sequence was used to develop a three-component reaction leading to functionalized β-amino alcohols **35** [29, 30]. The reaction used both ketones (specifically, acetone) and aldehydes **33** as donors, together with azodicarboxylate **34** (Scheme 42.9) [30]. The first step is the proline-catalyzed amination of aldehydes [31], leading to intermediate **36**, which represents the electrophilic substrate for the subsequent aldol reaction with acetone. Both intermolecular steps proceed under enamine catalysis by proline **1**. A key factor in the high level of chemoselectivity observed was the much higher reactivity of aldehyde over ketone in the proline-catalyzed α-amination reaction, which selectively forms **36**.



Scheme 42.9 Three-component reaction under an enamine–enamine activation sequence, with two intermolecular stereo-determining processes.

This example, although very interesting, could not exploit the full potential of an asymmetric MCR in which more than one catalytic event is under the control of the chiral organocatalyst. There was poor control over the relative stereochemistry, although the Horeau principle (see Figure 42.1 and discussion thereof) calls for a higher overall stereoselectivity of the whole process. The low level of

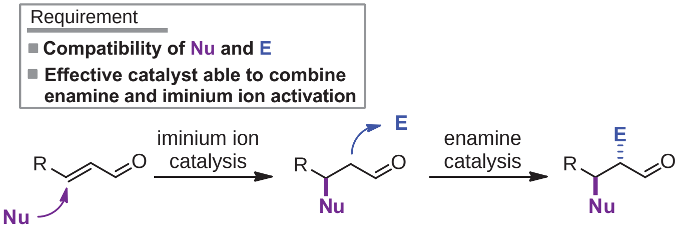

Requirement
Compatibility of Nu and E
Effective catalyst able to combine enamine and iminium ion activation
R
O
Nu
iminium ion catalysis
E
Nu
enamine catalysis
E
Nu

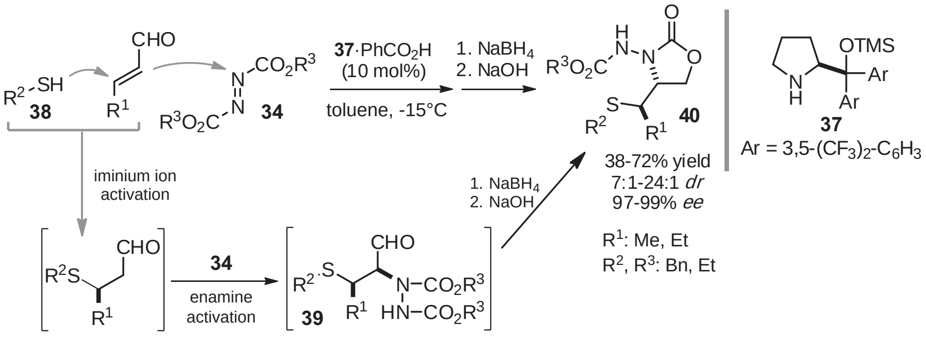
Figure 42.2 Iminium ion–enamine activation sequence; compatibility between the nucleophile (Nu) and the electrophile (E) is required.

diastereoselectivity was due to the inherent configurational instability of intermediate **36**, which, under the reaction condition, undergoes rapid racemization prior to its conversion into the final aldol product **35**.

To fully harness the synthetic power of aminocatalytic domino processes, it was crucial to identify the iminium ion–enamine activation sequence as an enabling approach to highly efficient MCRs. The strategy is based on the conjugated addition of a nucleophile to α,β-unsaturated aldehydes or ketones followed by α-functionalization of the resulting saturated carbonyls (Figure 42.2). In this well-defined sequence, the chiral amine catalyst has an active role in both steps, initially forming the activated iminium ion species and later the electron-rich enamine intermediate. The main reactivity issue to be addressed lies in identifying a nucleophilic and an electrophilic substrate that can coexist under the reaction conditions, without them interacting with each other through a competitive coupling.

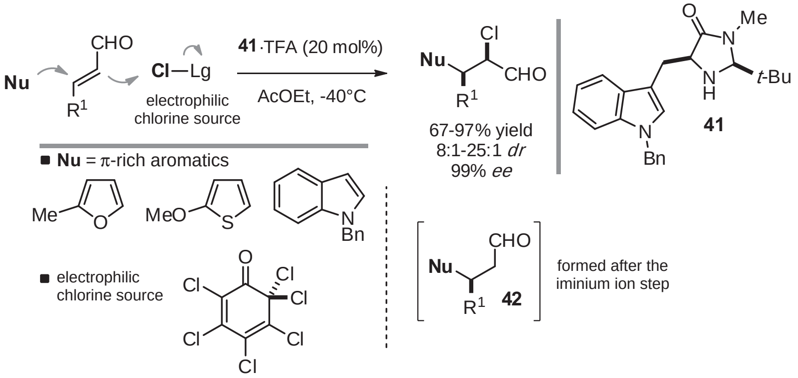
The feasibility of this aminocatalytic strategy, which combines two *intermolecular* and stereoselective bond-forming events, was independently established in 2005 by two research groups, those of Jørgensen [32] and MacMillan [33]. It has become common for challenging concepts in asymmetric aminocatalysis to be developed independently (and almost simultaneously) by different research groups. This accounts for the tremendous scientific competition, which has led to excellent levels of development and innovation in the field [34].

Jørgensen and coworkers combined the first highly enantioselective organocatalytic addition of thiols to α,β-unsaturated aldehydes with the α-amination reaction (Scheme 42.10) [32]. The catalyst of this tandem reaction, the diarylprolinol silyl ether **37**, belongs to the highly versatile catalyst class independently developed by Jørgensen [27a] and Hayashi [27b] (see the chemistry described in Schemes 42.7 and 42.8). Combining α,β-unsaturated aldehydes with a nucleophilic alkyl thiol (**38**) and the electrophilic azodicarboxylate (**34**) initiated a sulfa-Michael/amination sequence leading to products **39**. *In situ* $NaBH_4$ reduction and cyclization under basic conditions in a one-pot process afforded the cyclic adducts **40**, which had two adjacent stereocenters, in good yields and with excellent diastereomeric ratios and enantiomeric excess. Importantly, moderate to good yields could be maintained when all three components were part of the multicomponent reaction in an approximate 1 : 1 : 1 stoichiometric ratio.



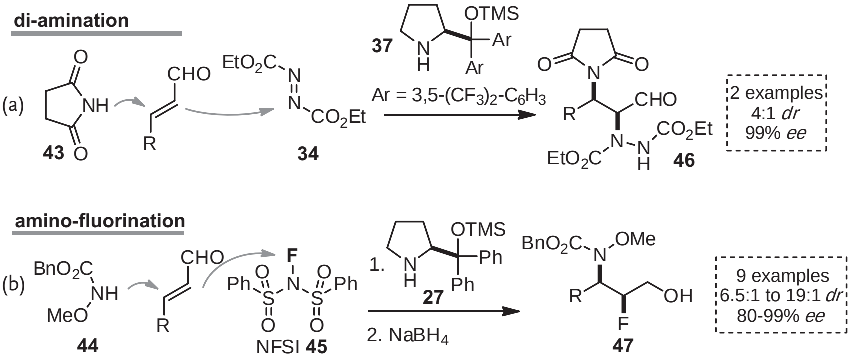
Scheme 42.10 Organocatalytic domino sulfa-Michael/amination process by way of an iminium ion–enamine sequence: both catalytic steps are intermolecular reactions. Protocol point: compound **34** was added after 30 min.

Almost simultaneously, MacMillan and colleagues developed a similar MCR based on the iminium ion–enamine activation of enals (Scheme 42.11) [33]. They used the chiral imidazolidinone catalyst **41** to combine the enantioselective conjugate additions of a large number of diverse carbon-based nucleophiles with the α-chlorination of the resulting aldehyde intermediate **42**, which proceeds under enamine catalysis [35]. The reaction sequence is accompanied by a high *syn*-selectivity and excellent enantioselectivities.



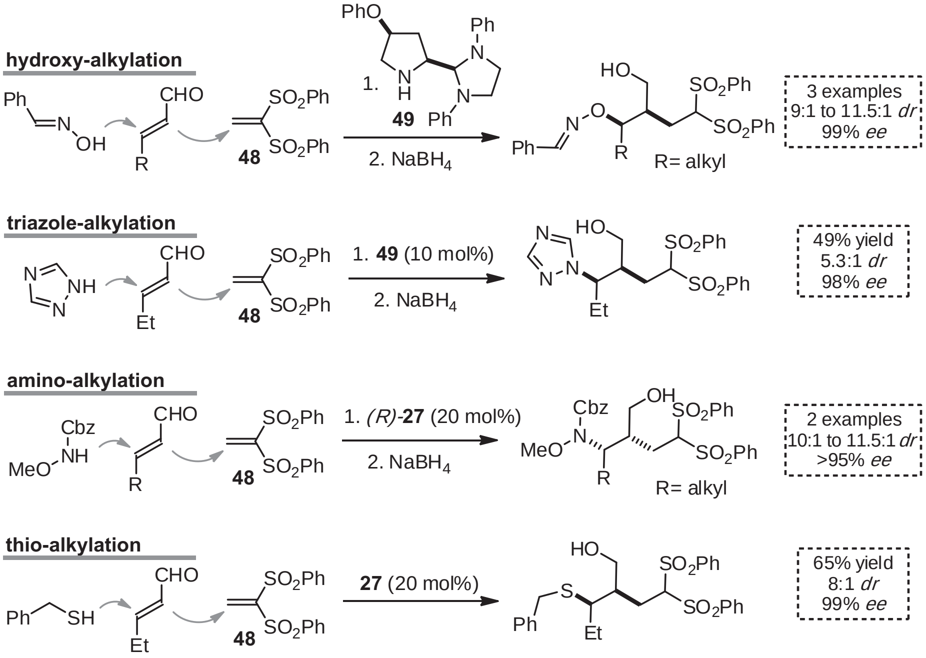
Scheme 42.11 Organocatalytic domino aryl/chlorination process by way of an iminium ion–enamine sequence: both catalytic steps are intermolecular reactions. Protocol point: all substrates added at the outset of the reaction.

In line with the previously discussed Horeau principle, the interaction between the chiral catalyst and the chiral intermediate, resulting from the first conjugated addition under iminium ion activation, induces a remarkable enantioenrichment in the final enamine step. As a result, the chemistry shown in Schemes 42.10 and 42.11 afforded rapid access to acyclic complex products with enantiomeric excess generally over 99% for the *syn*-diastereoisomer. These investigations showed the synthetic community that the iminium ion–enamine activation strategy is a highly efficient method for functionalizing enals at their α and β positions. It generates valuable acyclic aldehydes with two vicinal stereogenic centers in nearly optically pure form. As a consequence, many researchers took up the challenge of identifying other combinations of electrophiles and nucleophiles able to coexist under the MCR conditions. These efforts led to the development of useful methodologies, such as the di-amination [36] and the amino-fluorination [37] of enals, reported in Scheme 42.12a,b, respectively. Both processes exploited the ability of the diarylprolinol silyl ether derivatives to promote the domino process, leading to the corresponding functionalized products with very high stereoselectivity. The di-amination chemistry used a combination of a nucleophilic and an electrophilic nitrogen source, namely, succinimide **43** and the azodicarboxylate **34** [36], while the fluoro-amination was designed by combining hydroxylamine derivatives **44** with *N*-fluorobenzenesulfonimide (NFSI, **45**) [37]. The complex chemoselectivity issues arising from the particular substrate combinations were solved by adding the electrophilic reagent (**34**, or **45**) once the first iminium ion-driven aza-Michael reaction was complete. Although these reactions cannot be classified as MCRs, they provide synthetically useful diamino aldehydes **46** and α-fluoro-β-amino alcohols **47** (after *in situ* $NaBH_4$ of the aldehyde precursors).



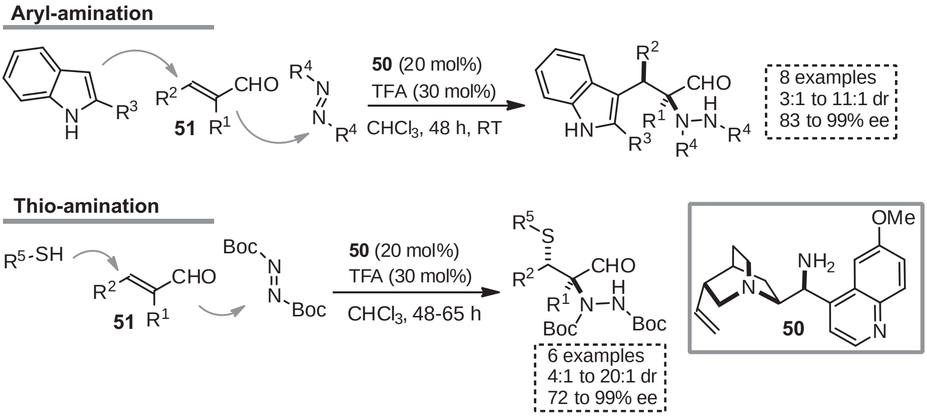
Scheme 42.12 Organocatalytic one-pot (a) di-amination and (b) amino-fluorination of enals by way of an iminium ion–enamine sequence. Protocol point: the electrophiles **34** and **45** are added once the aza-Michael addition of **43** and **44** to enals is over.

The above examples of iminium ion–enamine activation strategies of enals were all designed using a heteroatom-centered electrophile, with the enamine-catalyzed step generating a carbon–heteroatom bond. Recently, the high reactivity of vinyl sulfone **48** allowed the development of an MCR of enals in which the second bond-forming event forged a new C–C linkage. The strategy was effective with various distinct nucleophilic components. The hydroxy-alkylation, triazole-alkylation, amino-alkylation, and thio-alkylation of enals were efficiently carried out (Scheme 42.13), illustrating the potential and versatility of this approach for synthesizing attractive synthons in high enantioselectivity (typically 99% ee) [38]. The classic secondary aminocatalyst **27** (the Jørgensen–Hayashi catalyst) or the aminal pyrrolidine **49** were used to drive the MCRs.



Scheme 42.13 Organocatalytic MCRs of enals by way of an iminium ion–enamine sequence. Protocol point: hydroxy-alkylation: all substrates added at the outset of the reaction. In both the triazole- and amino-alkylation processes the vinyl sulfone **48** is added once the aza-Michael reaction is over. Thiol-alkylation: **48** is added after 20 min.

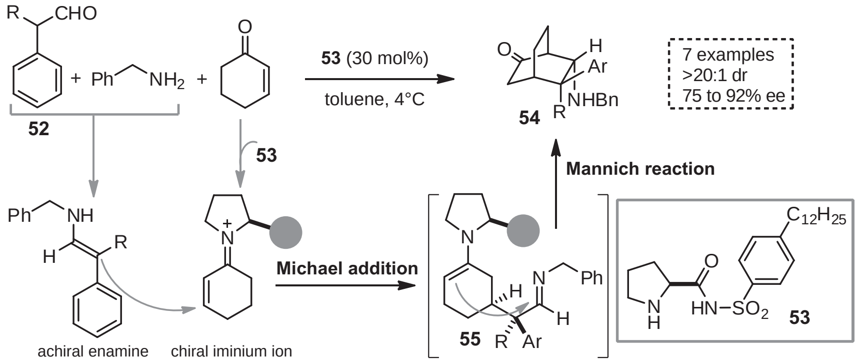
Subsequent investigations sought to extend the synthetic utility of the iminium ion–enamine-based domino reactions. They focused on more difficult carbonyl compounds. α-Branched α,β-unsaturated aldehydes have long been challenging substrates for asymmetric catalysis. Neither metal-based methodologies nor asymmetric aminocatalysis have provided a way to stereoselectively functionalize this sterically-congested compound class. Cinchona primary amines of type **50** have recently enriched the aminocatalysis toolbox. This is due to their unique ability to engage in iminium ion formation with encumbered enones while enforcing high geometry control and face discrimination [39]. In 2009, it was hypothesized that this ability could be translated to the challenging class of α,β-disubstituted enals. Researchers successfully developed two MCRs that combine two intermolecular and stereoselective steps (Scheme 42.14). The aryl-amination and thio-amination processes of α-branched enals **51** follow a defined Michael addition/amination



Scheme 42.14 Organocatalytic MCRs of α-branched α,β-unsaturated aldehyde enals by way of an iminium ion/enamine sequence: Friedel–Crafts/amination strategy and sulfa-Michael/amination strategy. Protocol point: all substrates added at the outset of the reaction.

pathway, where the indole or the thiol acts as the nucleophile and the azodicarboxylate as the electrophile [40]. The chemistry affords straightforward access to valuable precursors of α-amino acids that have two adjacent stereogenic centers with high optical purity.

Later, enones served as useful substrates for designing domino reactions. The multicomponent couplings of cyclohexenone, α,α-disubstituted aldehydes **52** and benzylamine, driven by the proline aryl sulfonamide catalyst **53**, led to densely functionalized [2.2.2] bicyclic ketones **54** containing up to four contiguous stereogenic centers in high enantio- and diastereoselectivity (Scheme 42.15) [41]. The chemistry is synthetically valuable because it addresses the difficult challenge of stereoselectively forging an all-carbon quaternary stereocenter in complex scaffolds [42]. The catalytic machinery is also conceptually intriguing. It successfully



Scheme 42.15 Organocatalytic MCRs of cyclohexenone: Michael/Mannich sequence.

combines the nucleophilic profile of the *in situ* generated achiral enamine, resulting from condensation of **52** and benzylamine, with a chiral iminium ion intermediate, acting as the electrophilic component. The catalyst-induced stereocontrolled conjugate addition afforded an imine adduct **55**, which is amenable to a further intramolecular aminocatalytic Mannich reaction under enamine activation, resulting in the complex products **54**.

The above is another example of the intense investigations carried out on secondary amine-catalyzed domino reactions by means of iminium ion–enamine activation. It illustrates again how researchers have been able to provide sophisticated solutions to difficult problems in organic chemistry. Recently, the MCR approach provided straightforward access to all possible stereoisomers of a cascade process individually.[1] This is an exceedingly challenging target because aminocatalytic domino reactions are based on the use of a single amine catalyst, which may give access to a limited set of diastereomers. The solution was to engineer cycle-specific catalysts characterized by different iminium ion–enamine activities [43]. These sophisticated strategies use two distinct yet compatible chiral secondary amines. Thus, they fall outside of the scope of this chapter, and are not described in detail.

42.2.3
Asymmetric MCRs Based on Three or More Aminocatalytic Steps

In developing aminocatalytic MCRs, it was crucial to recognize the unique ability of chiral secondary amines to integrate orthogonal activation modes of aldehydes (enamine and iminium ion catalysis) into more elaborate reaction sequences. One high point of the innovations and progress within the field was the triple organocascade reaction, developed in 2006 by Dieter Enders and colleagues [44]. Exploiting the catalytic behavior of the chiral secondary amine **27**, they developed an outstanding enamine–iminium ion–enamine sequential activation of aldehydes **56**, nitroalkenes **57**, and α,β-unsaturated aldehydes **58**, resulting in cyclohexene aldehydes **59** with four stereocenters in essentially enantiomerically pure form (Scheme 42.16). The three-component domino strategy proceeds by way of a catalyzed Michael/Michael/aldol condensation sequence. It is based on an operationally trivial procedure that uses unmodified, cheap, and commercially available starting materials and catalyst while achieving exquisite levels of stereocontrol. The triple organocascade proved flexible enough to provide simple direct access to a library of complex cyclic derivatives **59**, with four stereocenters, in enantiomerically pure form.

Despite its operational simplicity (all the reagents were mixed together in the presence of the catalyst and without any precautions for excluding moisture from the reaction vessel), the mechanism of the triple organocascade (depicted in

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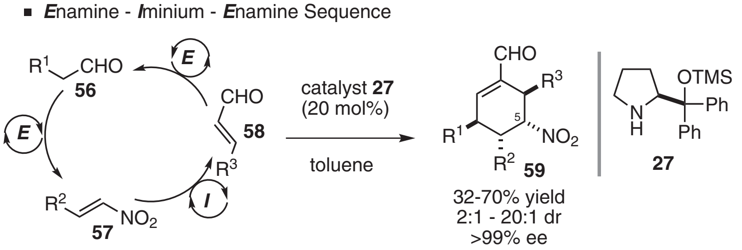
1) Achieving the full matrix of all possible stereoisomeric products of a domino reaction is exceedingly challenging. This is because the ability of a catalyst to modify the intrinsic diastereoface preference of a reaction involving a chiral substrate is a largely unsolved issue.



Scheme 42.16 Asymmetric organocatalytic triple cascade by way of an enamine–iminium ion–enamine activation of aldehydes. Protocol point: the minor diastereomer was determined as the 5-epimer of **59;** all substrates added at the outset of the reaction.

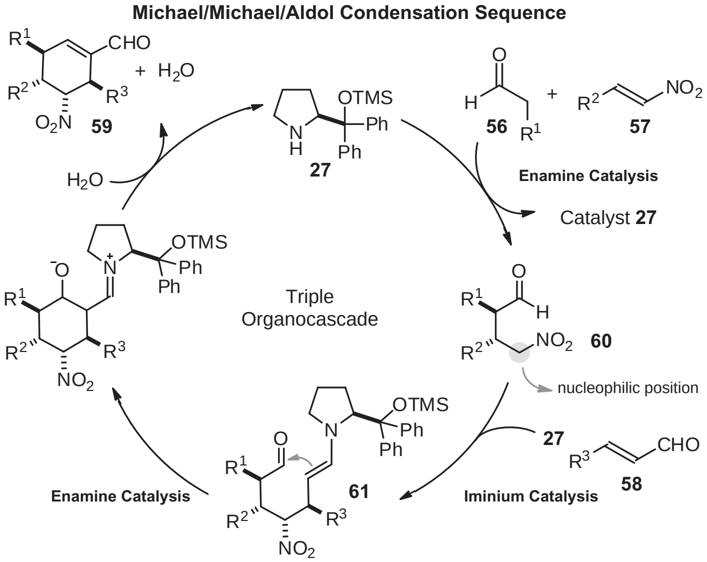
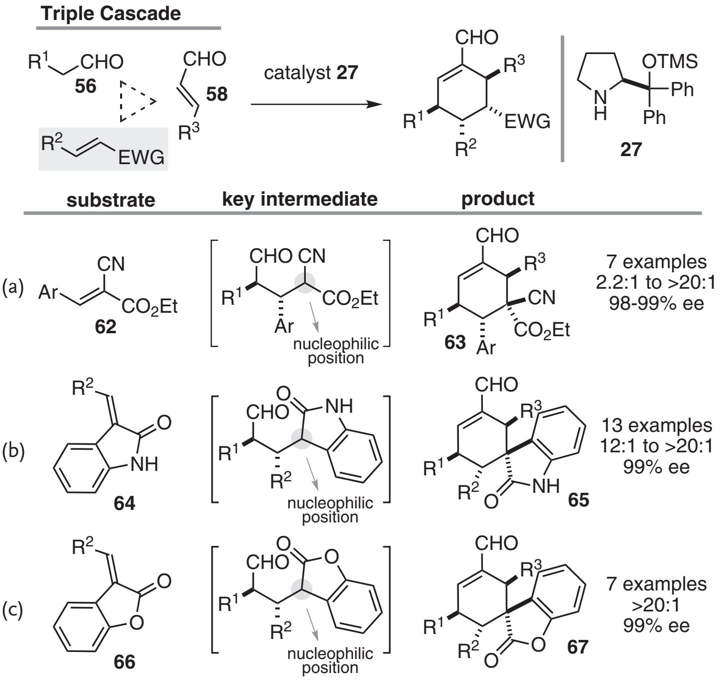


Figure 42.3 Catalytic machinery of the Enders triple organocascade.

Figure 42.3) is based on highly regulated and sophisticated catalytic sequences. The aminocatalyst **27** first controls an enamine-catalyzed Michael addition of aliphatic aldehydes **56** to nitrostyrene derivatives **57**. In the second step, the chiral amine, by way of the iminium ion activation of α,β-unsaturated aldehydes **58**, promotes an intermolecular conjugate addition of the transiently generated nitroalkane nucleophilic intermediate **60**. The last step is an intramolecular enamine-catalyzed aldol reaction, where the less hindered aldehyde of intermediate **61** acts as a nucleophile, followed by the elimination of water. The impressive chemo- and stereo-selectivity, which catalyst **27** may infer, was critical to implementing the strategy. But other factors were essential too. The catalytic machinery required the Michael acceptor, namely, the nitroalkenes **57**, to address several specific issues. Initially, **57** must intercept the enamine intermediate, generated by catalyst condensation with aldehyde **56**, much faster than the unsaturated carbonyl compounds do (aldehyde **58** or the corresponding activated iminium intermediate). The resulting conjugate adduct **60** has to act as a prochiral carbon nucleophile that can selectively engage in the iminium ion-catalyzed conjugate addition to **58**.

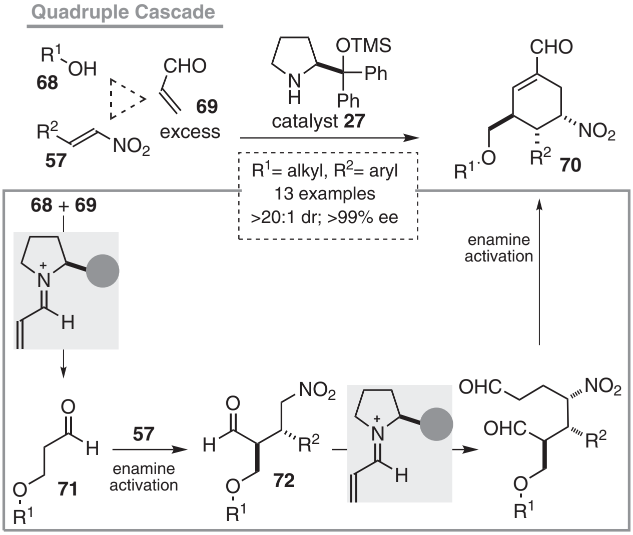
The triple cascade by Enders and colleagues represents a most spectacular example of the potential of secondary amine-mediated MCRs to target stereochemical and molecular complexity. This report provided the chemistry community with a new foundation for developing reactions. By appropriately combining the reaction components, including the aminocatalyst **27** and the aldehydic partners **56** and **58** to preserve the catalytic machinery of the original triple organocascade sequence, researchers have a reliable synthetic platform for targeting difficult problems connected with the preparation of complex chiral molecules. The challenge was to identify suitable compounds that could mimic the reactivity behavior of the nitroalkene. The compounds needed to first act as a Michael acceptor and then to originate, after the initial conjugate addition, a nucleophilic intermediate able to continue the cascade. Replacing derivatives **57** with cyanoacrylates **62** resulted in a triple organocascade that allows for the direct installation of all-carbon quaternary stereogenic centers in complex organic molecules [42] such as **63**, a difficult synthetic problem (Scheme 42.17a) [45].



Scheme 42.17 Synthetic potential of the triple organocascade: (a) forging all-carbon quaternary stereocenters, (b) and (c) construction of highly strained spirocyclic structures. The key nucleophilic intermediate is transiently generated after the enamine-catalyzed conjugate addition of **56**. Protocol point: all substrates added at the outset of the reaction.

The triple cascade also provided straightforward access to natural-product-inspired compound collections that would be difficult to synthesize by other enantioselective methods. Spiro-oxindole and spiro-benzofuranone cores, for example, feature in several natural products as well as medicinally relevant compounds [46]. However, their stereocontrolled synthesis, particularly installing the challenging spiro-quaternary stereocenter, is very difficult. Only a few venerable asymmetric transformations, such as cycloaddition processes and the intramolecular Heck reaction [47], had proven suitable for achieving this. By including compounds **64** or **66** as the third component of an organocatalytic MCR strategy, a direct, one-pot synthesis of complex spirocyclic oxindole [48] and benzofuranone [49] derivatives **65** and **67**, respectively, was developed (Scheme 42.17b,c). The spiro-cyclohexane architecture was constructed with the simultaneous creation of three bonds and four stereogenic centers in a single chemical step, while achieving exquisite levels of stereocontrol (only one stereoisomer out of the 16 possible: complete diastereo- and enantioselectivity, i.e., de >99%, ee >99%).

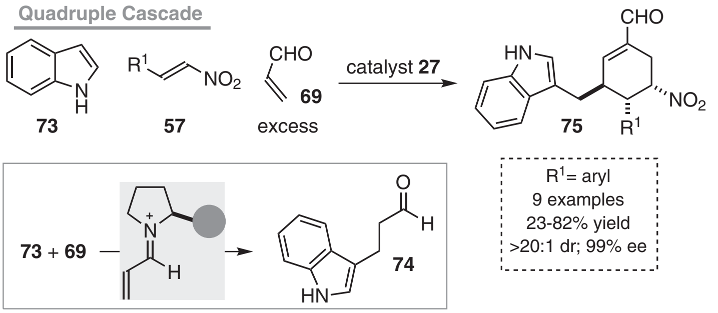
These examples highlight the ability of the triple organocascade to generate high degrees of stereochemical and architectural complexity in a single chemical transformation. The triple cascade's conceptual and catalytic principles provided the guidelines for the design of even more sophisticated MCRs. A three-component, quadruple cascade was developed by mixing an alcohol **68**, an excess of acrolein (**69**), and nitroalkenes **57** in the presence of catalyst **27** (Scheme 42.18) [50]. The reaction follows a highly regulated domino oxa-Michael/Michael/Michael/aldol condensation sequence through successive iminium ion–enamine–iminium



Scheme 42.18 Quadruple cascade reaction by way of an iminium ion–enamine–iminium ion–enamine activation of aldehydes. Protocol point: all substrates added at the outset of the reaction.

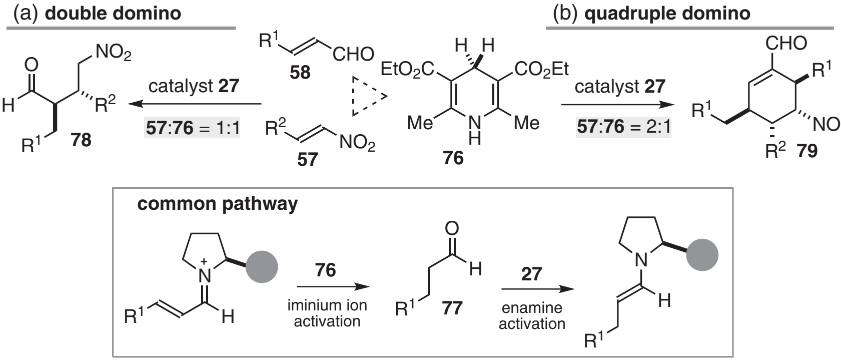
ion–enamine activation, leading to highly functionalized trisubstituted cyclohexene carbaldehydes **70**. The key to success was the complete chemoselectivity and high reactivity of the first oxa-Michael addition of alcohol **68** to acrolein **69** under iminium ion activation. The resulting intermediate **71** can play the role of the aldehyde component, thus entering the original machinery inherent to the triple cascade by way of an enamine-driven attack on the nitroalkene derivative **57**. The generated prochiral carbon nucleophile **72** can attack another molecule of acrolein **69**, thus continuing the quadruple cascade. Two aspects are noteworthy: (i) the dual role of acrolein, which serves twice as the electrophilic partner of the domino sequence, and (ii) the chemoselective preference of the aldehyde intermediate **71** to undergo an enamine-catalyzed addition to the nitroalkene **57** (instead of a possible addition to acrolein).

Enders and colleagues developed a similar quadruple cascade, where three intermolecular Michael reactions and one intramolecular aldol condensation are combined [51]. Again, the high reactivity of acrolein **69** is crucial. The process starts with the first iminium-mediated Friedel–Crafts alkylation of indoles **73** with **69**, a fast step that is strongly favored over the competing addition to nitroalkene **57** (Scheme 42.19). The generation of aldehyde **74** provides the intermediate required for the subsequent triple cascade. The chemoselective enamine addition of **74** to nitroalkenes **57** is secured by slowly adding acrolein in order to minimize the possible addition of **74** to acrolein. This chemistry provides straightforward and efficient access to 3-(cyclohexenylmethyl)indoles **75**, with three stereogenic centers, in moderate to excellent yields and excellent stereoselectivities.



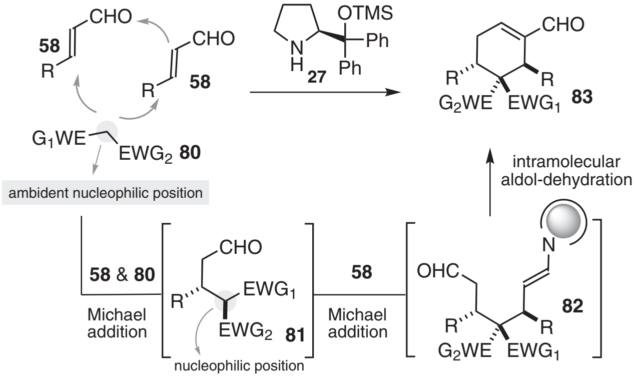
Scheme 42.19 Enders quadruple cascade reaction. Protocol point: acrolein (**69**) added slowly over 12 h (syringe pump addition).

By intensively studying the triple organocascade of aldehydes and nitroalkenes, researchers have been able to elucidate and appreciate the reactivity and mechanism of its individual processes. This has led to a more complex MCR, where the course of the domino reaction is controlled and altered simply by modulating the substrate concentration [52]. Two completely distinct domino processes were produced by combining different amounts of α,β-unsaturated aldehyde **58** with nitroalkenes **57** and Hantzsch dihydropyridine **76** as an hydride delivery agent in the presence of diphenylprolinol silyl ether **27** as the catalyst (Scheme 42.20). Both processes are initiated by the iminium ion-catalyzed chemoselective reduction of enal **58**. This results in aldehyde **77** that, upon formation of the enamine, may engage in a Michael addition step with the nitroalkene **57**. When using an equimolar amount of enal **58** and Hantzsch dihydropyridine **76**, the Michael adduct **78** is the final product of a domino reaction that follows an iminium ion–enamine tandem sequence (path a in Scheme 42.20). However, if there is an excess of **58** (2 : 1 ratio with respect to **76**) it may serve as the electrophilic Michael acceptor required for continuing the triple organocascade. Under these conditions, **78** acts as a nucleophilic intermediate and not as a final product. It engages in an iminium ion–enamine sequence that leads to cyclic products **79**, which are the compounds achieved in the original triple cascade (path b, Scheme 42.20).



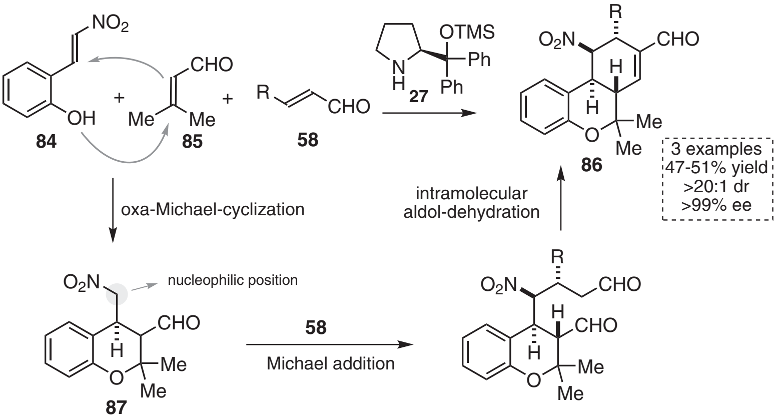
Scheme 42.20 Changing the fate of a domino process by modulating the concentration of enal **58**: (a) double domino reaction by means of an iminium ion–enamine activation sequence; (b) quadruple domino reaction by means of an iminium ion–enamine–iminium ion–enamine activation sequence. The shaded circle represents the catalyst scaffold.

The versatility and regulated chemoselective machinery of the Enders triple cascade offers an unparalleled template for developing aminocatalytic asymmetric MCRs. The search for mechanistically distinct domino processes has met with limited success, mainly due to the difficult chemoselectivity issue connected with systems in which more than two substrates are combined. An explanatory example is provided with the triple domino reaction depicted in Scheme 42.21. The ambident nucleophilic profiles of activated methylene compounds **80** provided the possibility of designing a domino reaction, again exploiting the versatility of catalyst **27** to activate enals **58** through iminium ion formation. The first Michael addition step generates a prochiral carbon nucleophile **81**, which is reactive enough to initiate a second, intermolecular, iminium ion-catalyzed conjugate addition with another molecule of **58** to afford intermediate **82**. The last intramolecular aldolization–dehydration sequence, driven by enamine catalysis, eventually affords the cyclohexene aldehyde **83**. Given the variety of different substrates that may act as the nucleophilic component **80**, this reaction sequence has been widely used to rapidly construct stereochemically dense cyclohexenyl rings adorned with different molecular architectures and with high stereocontrol [53]. However, the difficulties in differentiating the reactivity of distinct enals **58** (i.e., to achieve chemoselectivity) have relegated this chemistry to the field of two-component domino reactions.



Scheme 42.21 Two-component domino reactions by means of an iminium ion–iminium ion–enamine activation sequence. The shaded circle represents the catalyst scaffold.

A recent inspiring contribution shows how, by identifying the chemo-differentiating reactivities inherent to enals **58**, researchers can design more sophisticated and higher-order aminocatalytic domino reactions. Combining 2-[(*E*)-2-nitrovinyl]phenol (**84**) with enal **58** and 3-methylbut-2-enal (**85**) in the presence of aminocatalyst **27** resulted in a domino oxa-Michael/Michael/Michael/aldol condensation leading to products **86** (Scheme 42.22) [54]. This effective quadruple-cascade and multicomponent organocatalytic reaction created three new C–C bonds while forging up to five stereocenters with high fidelity, a stereochemical density never reached before in aminocatalytic MCRs (the triple cascade creates four stereocenters). The key mechanistic point was the premature termination of the domino sequence when using the encumbered enal **85**. Specifically, the oxa-Michael/cyclization sequence under iminium ion–enamine activation very rapidly led to intermediate **87**. This nucleophilic intermediate may engage in a further iminium ion-promoted Michael addition step, in principle with another molecule of enal **85**. However, steric effects completely inhibited this pathway, allowing the design of a more complex sequence when using a different enal **58**. Enal **85** can undergo an extremely fast oxa-Michael-cyclization sequence while remaining completely unreactive towards the second Michael addition. It was this unique chemoselective behavior that allowed researchers to engineer an effective MCR.



Scheme 42.22 Quadruple domino reaction by means of an iminium ion–enamine–iminium ion–enamine sequence. Five stereocenters are forged when a two-component reaction is operative (in the presence of two equivalents of **58** and the absence of **85**).

42.2.4
One-Pot Asymmetric MCRs for the Preparation of Active Pharmaceutical Ingredients

Given the potential of aminocatalytic asymmetric MCRs to generate structurally and stereochemically complex molecule skeletons with appropriate efficiency, scale, purity, and cost and in a very short period of time, this synthetic strategy may positively impact the drug-discovery field. This is because it allows the preparation of a wide range of enantiopure compound libraries spanning large tracts of biologically relevant chemical space that may increase the probability of success in identifying drug-candidate structures [55]. Although this possibility has not been fully explored yet, recent reports have demonstrated how the integration of aminocatalytic MCRs in uninterrupted sequences of one-pot transformations can be used for streamlining the preparation of active pharmaceutical ingredients [56]. Even if those strategies cannot be classified as multicomponent domino reactions, since they require temporarily distinct addition of reagents or removal of volatiles from the reaction vessel by distillation, the approach testifies to the potential of aminocatalytic domino sequences as enabling methods for the one-pot synthesis of biologically relevant targets.

Hayashi and colleagues recently succeeded in carrying out the multistep synthesis of the dipeptidyl peptidase IV (DPP4) selective inhibitor ABT-341 (**88**) in one single pot (Scheme 42.23) [57]. This study followed the development by the same research group of a two-pot procedure [58] for the preparation of a marketed chiral drug, namely, (–)-olsetamivir (Tamiflu, **89**) [59]. As shown in Figure 42.4, the structures of the target molecules **88** and **89** both have a remarkable resemblance to the cyclohexene scaffold generated by the Enders triple organocascade (product **59**). Indeed, this chemistry provided again a suitable reactivity platform

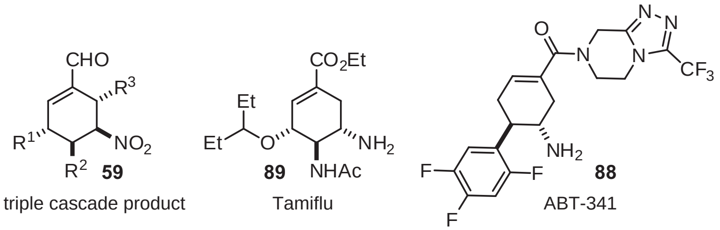
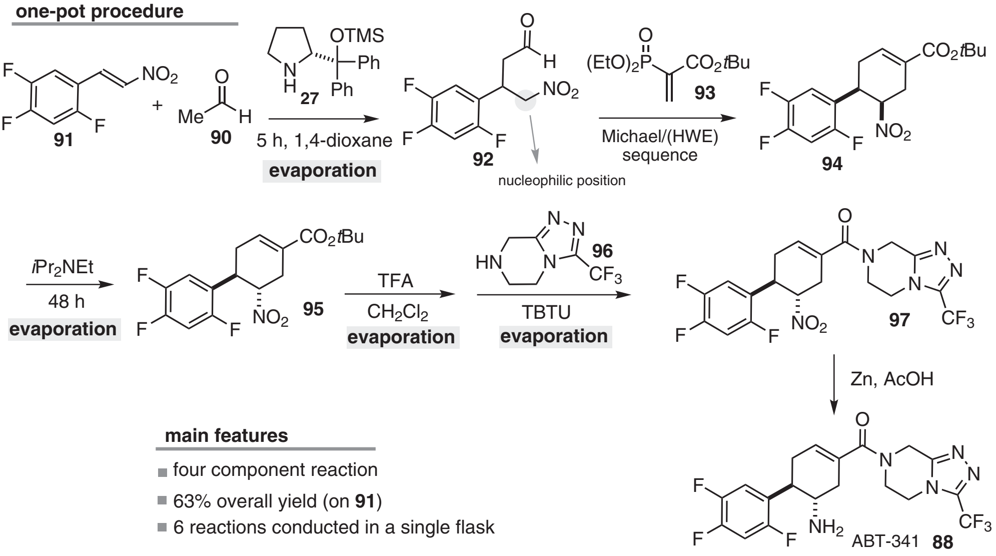


Figure 42.4 Structural similarities among the triple cascade adducts **59** and the active pharmaceutical compounds **88** (ABT-341) and **89** (Tamiflu).



main features

- four component reaction
- 63% overall yield (on **91**)
- 6 reactions conducted in a single flask

Scheme 42.23 One-pot synthesis of ABT-341 in an uninterrupted sequence of reactions. Protocol point: the strategy requires careful choice of low-boiling reagents and solvents, to avoid possible detrimental interactions with successive chemical steps; four evaporations were required during the one-pot synthesis. [TBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate].

and the key catalytic machinery for the successful implementation of the Hayashi strategies.

As detailed in Scheme 42.23, the one-pot synthesis of ABT-341, potentially useful in the therapy for type 2 diabetes, was designed around the highly stereoselective Michael addition of acetaldehyde **90** to nitroalkene **91** catalyzed by the Jørgensen–Hayashi catalyst (*R*)-**27**. Then, exploiting the reactivity of the resulting nucleophilic intermediate **92**, a domino transformation was carried out: the addition of the vinylphosphonate **93** starts a Michael/intramolecular Horner–Wadsworth–Emmons (HWE) ring closure sequence, yielding intermediate **94**.

After a base-promoted epimerization leading to **95**, *tert*-butyl ester cleavage (with TFA) and TBTU-mediated amide formation with amine **96** gave the intermediate **97**. Reduction of the nitro group and purification by chromatography afforded the target compound **88** in a one-pot operation.

42.3
Non-Covalent Modes of Catalysis

42.3.1
Introduction

When compared to covalent enantioselective organocatalysis, its non-covalent counterpart is a less mature discipline. This is unsurprising. Researchers only recently developed the two conceptually related approaches that have dominated non-covalent organocatalysis. In 2004, Uraguchi and Terada [60], and Akiyama *et al.* [61], independently reported pioneering studies on ion pairing and the use of chiral counterions. The two groups studied the use of chiral phosphates as anions for iminium species in Mannich and Mannich-type reactions, respectively (chiral Brønsted acid catalysis). A complementary strategy was developed by Jacobsen and coworkers, who pioneered the use of thiourea catalysts as H-bond donors for the selective stabilization of anions. In 1998, they published the first example of this novel catalytic activation mode, an asymmetric addition of cyanides to imines (the Strecker reaction) [62]. However, it took some years for the generality of the concept to be realized [63]. Nowadays, thiourea organocatalysts are applied in asymmetric synthesis with increasing frequency [64].

In contrast to conventional reaction setups, multicomponent approaches require a significantly higher level of chemoselectivity. Therefore, applications of enantioselective non-covalent organocatalysis in reactions of three and more components still remain limited in number. The potential of catalysts with a non-covalent mode of action to overcome the inherent difficulties of multicomponent reactions to be performed stereoselectively, however, makes these transformations particularly worthy of investigation. This section focuses on recent successes in this direction.

Certain structural requirements limit the possibility of performing a multicomponent reaction enantioselectively using non-covalent organocatalytic activation modes. To use chiral Brønsted acids, a basic intermediate is needed for protonation. In addition, solvents must be chosen that allow an ion pairing of the chiral, often a bulky anion tight enough to exert efficient blocking of one of the two enantiotopic faces of the cation. For thiourea catalysis to be effective, one has to control H-bonding to a suitable acceptor, typically a reactive electrophile. Again, care must be taken over the solvent choice. This is because some polar media may greatly disrupt hydrogen bonds. With the above in mind, several multicomponent reactions have already been rendered enantioselective by means of thiourea or chiral Brønsted acid catalysis. In certain transformations, imines are formed in the course of the reaction and subsequently attacked by nucleophiles or involved in pericyclic reactions. These have special potential to be run asymmetrically because Schiff bases can easily be protonated by strong Brønsted acids such as phosphoric acids (Scheme 42.24). Alternatively, the nucleophilic attack to the carbonyls that characterizes many multicomponent reactions can also be spatially controlled by means of chiral thiourea catalysts. This approach can thus complement protonation with strong acids. Scheme 42.24 provides an overview of the applications of these general strategies in the implementation of asymmetric MCRs.

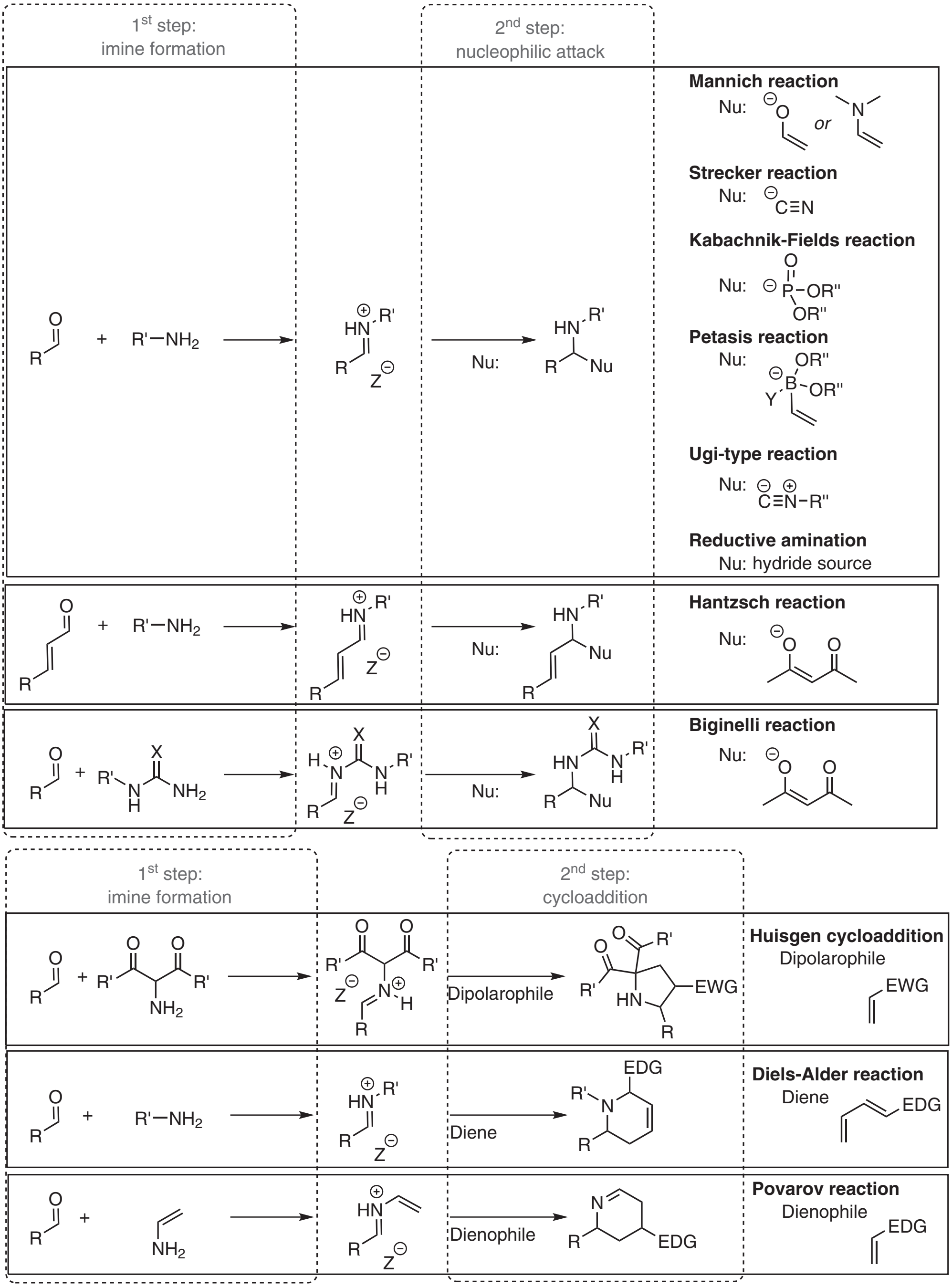
Using either of the two non-covalent catalytic modes of activation several multicomponent reactions could be performed with unprecedented selectivity and/or in a metal-free fashion for the first time. Figure 42.5 gives an overview of organocatalysts with a non-covalent mode of action that have already been successfully applied in asymmetric multicomponent reactions and which will be discussed in the following section.

42.3.2
Mannich Reactions

When Mannich and Krösche reported the condensation of formaldehyde, ammonia, and antipyrine, they probably did not realize the impact their findings would have on organic chemistry. However, they had just discovered what is now one of the most widely used methods for making β-amino carbonyl compounds [65]. Numerous applications of the Mannich reaction have been described to date, including catalytic asymmetric variants [66]. As mentioned above, the Mannich reaction was the first application of chiral phosphoric acids in asymmetric catalysis. At the time, it was studied with preformed imines. It was then another three years for the first three-component Mannich reaction to be developed by using a non-covalent mode of catalysis. In 2007, Gong and colleagues reported on the condensation of cyclic and acyclic ketones **116** with anilines **115** and aromatic aldehydes **114** using chiral phosphoric acid catalysts in very low loadings (Scheme 42.25). The products **117** were obtained with high *anti*-selectivity and with yields and enantioselectivities that ranged from moderate to excellent values [67].

Sickert and Schneider reported a vinylogous Mannich reaction that can be performed efficiently in a domino three-component fashion using the chiral phosphoric acid catalyst **100a** (Figure 42.5). Using substituted benzaldehyde **118**, anisidine (**119**), and a silyl-protected dienolate (**120**) the corresponding δ-amino-α,β-unsaturated carboxylic ester **121** was obtained regioselectively, in high yield and with very good enantioselectivity (Scheme 42.26) [68].

Masson and Zhu's group used enecarbamates **124** as nucleophiles in the Mannich reaction to access the synthetically valuable 1,3-diamine framework (Scheme



Scheme 42.24 Overview of multicomponent reactions rendered enantioselective by non-covalent organocatalysis. Conceptually, these approaches rely either on (i) protonation of an imine species formed in the course of the reaction using a chiral Brønsted acid or (ii) H-bond donation of a chiral thiourea moiety to heteroatoms directing a nucleophilic attack or a cycloaddition.

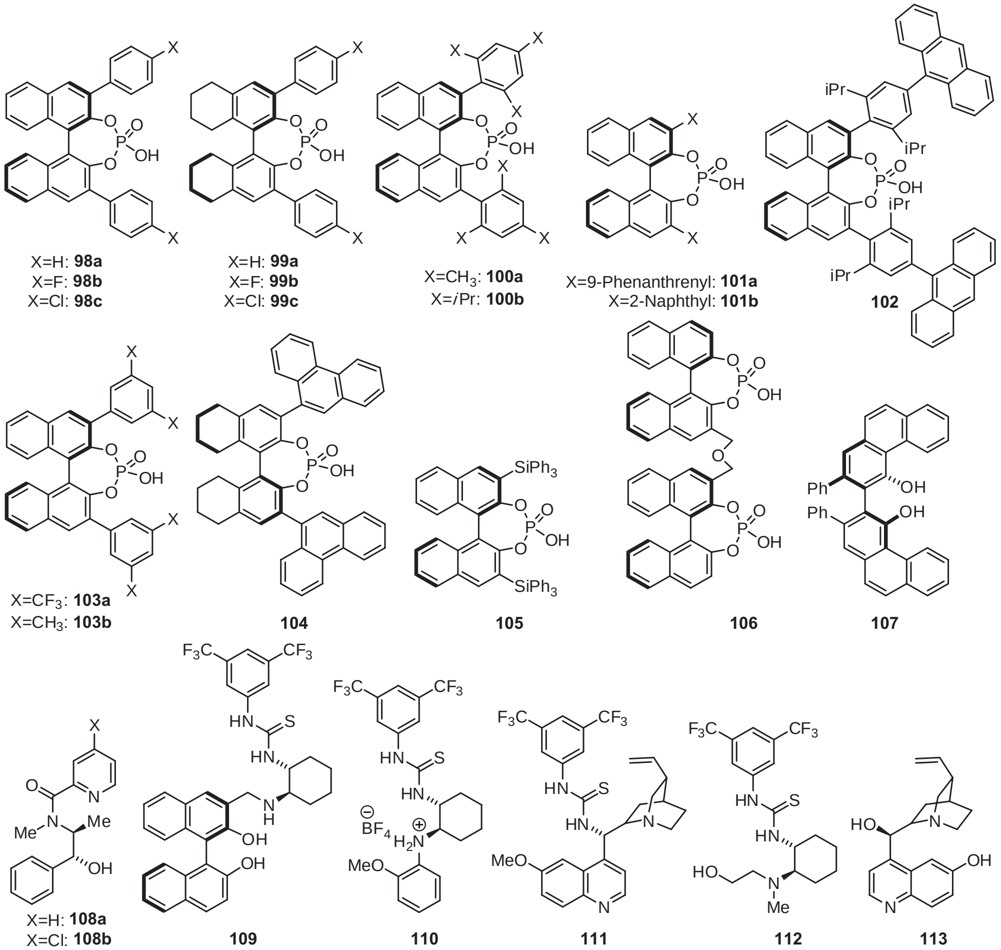
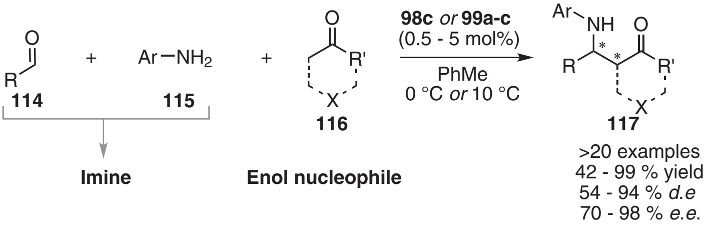
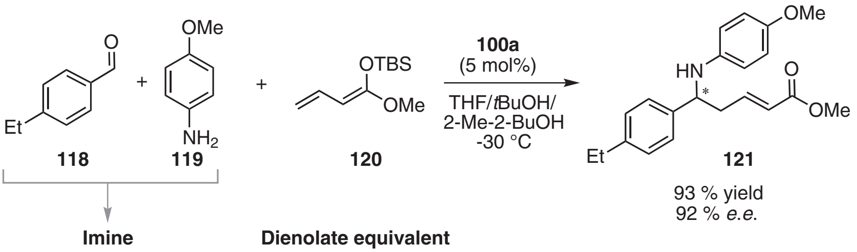


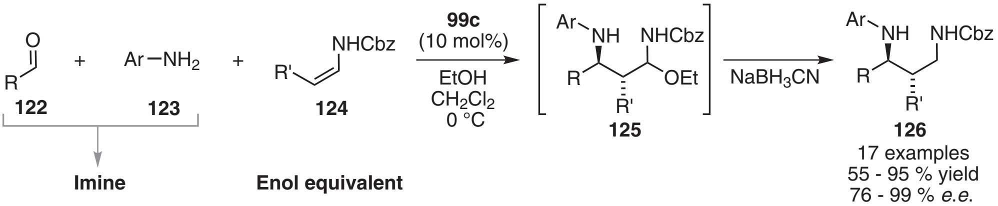
Figure 42.5 Non-covalent activation mode-based organocatalysts useful for enantioselective multicomponent reactions.



Scheme 42.25 Domino three-component Mannich reaction catalyzed by phosphoric acids.



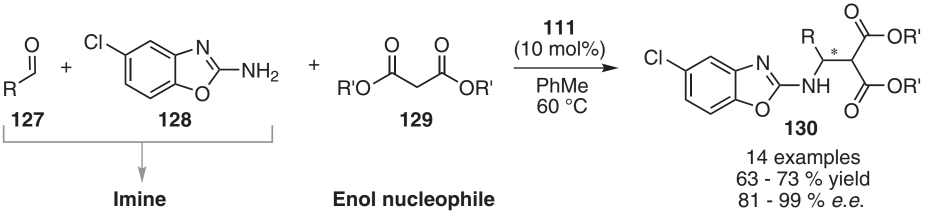
Scheme 42.26 Domino three-component vinylogous Mannich reaction catalyzed by a phosphoric acid.



Scheme 42.27 Sequential three-component Mannich reaction of aldehydes **122**, anilines **123**, and enecarbamates **124** for the synthesis of 1,3-diamines **126**.

42.27). Their reaction setup requires the conversion of aldehyde **122** and aromatic amine **123** into the imine prior to treatment with catalyst **99c** (a phosphoric acid) and enecarbamate (and a final reduction of the hemiaminal intermediate **125**). This three-component reaction can thus be classified as a sequential reaction. Notably, the authors also used aliphatic aldehydes successfully. Using substituted enecarbamates gave 1,2-disubstituted 1,3-diamines **126** with excellent *anti*-selectivity. They proposed a transition state in which the chiral phosphoric acid activates not only the imine as a Brønsted acid, but also the (*E*)-enecarbamate as Brønsted base, resulting in a *pseudo*-intramolecular *Si*-face attack to the imine [69].

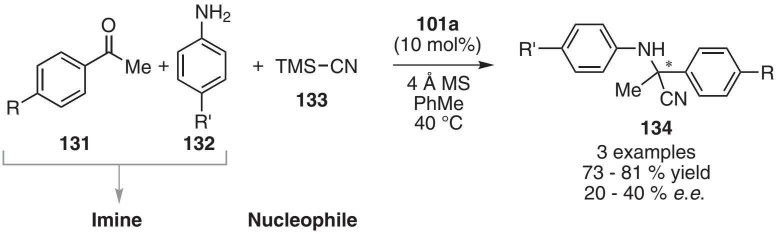
Very recently, Song, Yang, and coworkers described a domino Mannich reaction catalyzed by a chiral thiourea derivative of a cinchona alkaloid (**111** in Figure 42.5). They showed how amino-benzoxazoles **128** are viable amine components for the imine formation with aldehydes **127** in three-component Mannich reactions (Scheme 42.28) [70].



Scheme 42.28 Domino three-component Mannich reaction using aminobenzoxazoles as amine components for the synthesis of compounds **130**.

42.3.3
Strecker Reactions

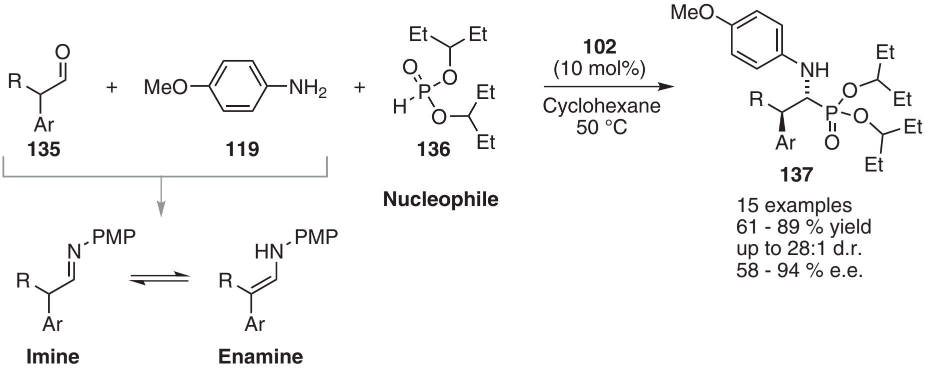
The Strecker reaction is one of the oldest in organic synthesis. It involves a three-component coupling of a carbonyl compound, an amine, and hydrogen cyanide to afford α-amino nitriles [71]. As these, in turn, allow the straightforward hydrolysis to the corresponding α-amino acids, the Strecker reaction has been of great value to organic synthesis ever since its discovery [72]. Great efforts to develop asymmetric Strecker reactions have also led to groundbreaking organocatalytic protocols for the conversion of preformed imines with cyanides [73]. However, there is only one report of the corresponding three-component reaction using aldehydes and amines as direct imine precursors, generating α-aminocyanides **134**. In 2010, Ma and colleagues reported a domino three-component Strecker reaction of ketones **131**, anilines **132**, and trimethylsilyl cyanide **133** catalyzed by the phosphoric acid **101a** (Scheme 42.29). However, the enantioselectivity remained modest (<40% ee) [74].



Scheme 42.29 Domino three-component asymmetric Strecker reaction.

42.3.4
Kabachnik–Fields Reaction

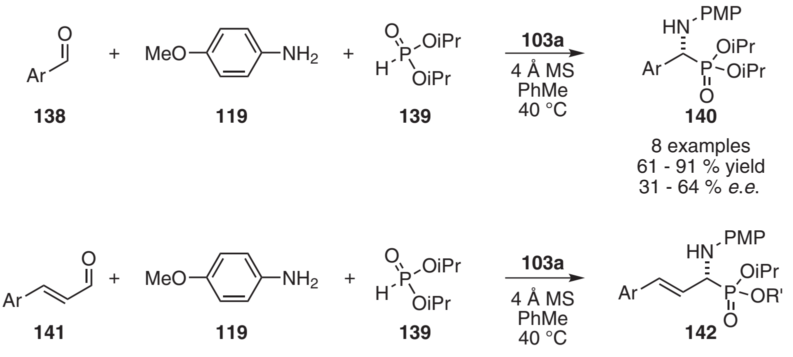
The Kabachnik–Fields reaction is a three-component hydrophosphonylation of imines formed in the reaction mixture from carbonyl compounds and amines [75]. In 2008, List and coworkers reported on such a reaction catalyzed by chiral phosphoric acids that combines a dynamic kinetic resolution with the concomitant generation of a new stereogenic center (Scheme 42.30). The resolution is possible when chiral racemic aldehydes **135** are used. This is because the imine formed in the first step of the reaction is in equilibrium with its achiral enamine tautomer, thereby racemizing the starting material continuously. Since one of the two enantiomers is selectively activated by the chiral phosphoric acid catalyst, the addition of phosphite **136** affords the exclusive formation of one diastereomer. All phosphonate products **137** were obtained with good yields and moderate to excellent diastereo- and enantioselectivity [76].



15 examples
61 - 89 % yield
up to 28:1 d.r.
58 - 94 % e.e.

Scheme 42.30 Domino three-component asymmetric Kabachnik–Fields reaction involving a dynamic kinetic resolution for α-branched aldehydes.

More recently, similar transformations using achiral aldehydes, anisidine (**119**), and phosphites **139** were reported by Ma's group, who further expanded the substrate scope to various substituted benzaldehydes **138** and cinnamaldehydes **141**, respectively (Scheme 42.31). Using the similar organocatalyst **103a**, the chiral α-aminophosphonates **140** and **142** were obtained in good yields and with modest to good enantioselectivity [77].



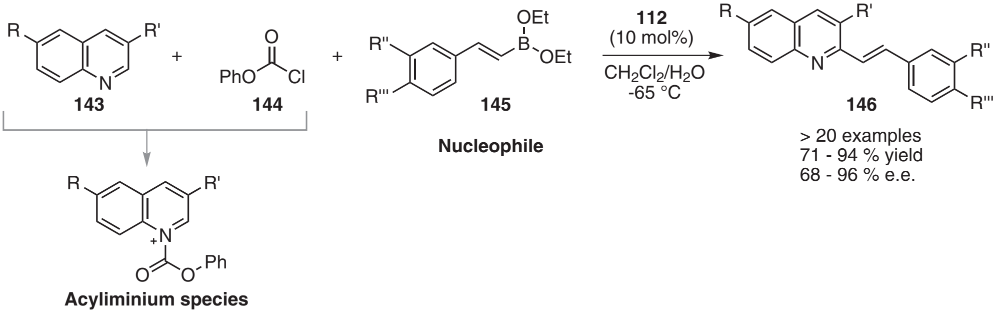
8 examples
61 - 91 % yield
31 - 64 % *e.e.*

6 examples
62 - 85 % yield
59 - 87 % *e.e.*

Scheme 42.31 Asymmetric domino three-component Kabachnik–Fields reaction using substituted benzaldehydes and cinnamaldehydes.

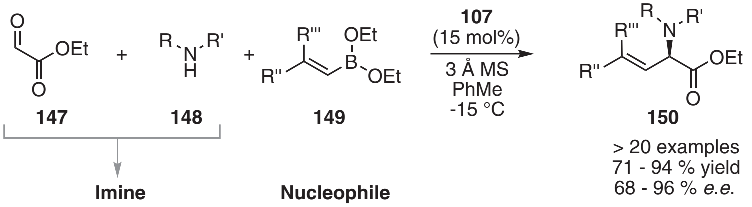
42.3.5
Petasis Reaction

In 1993, Petasis and Akritopoulou described the addition of vinyl boronic acids to formaldimine, leading to tertiary allylic amines [78]. Owing to the mild reaction conditions employed and the environmentally and toxicologically benign nature of the process, the Petasis reaction (or *borono*-Mannich reaction) has received great attention from both industry and academia [79]. Great progress toward a general asymmetric Petasis reaction was made by Takemoto and coworkers who reported the first enantioselective organocatalytic Petasis-type reaction of quinolines **143** and vinyl boronates **145** using chiral thiourea catalyst **112** and chloroformates **144** as stoichiometric activating agents (Scheme 42.32). This reaction is not a genuine multicomponent reaction since the activating component, which fulfills the purpose of acylating the quinoline at nitrogen, does not end up in the product [80].



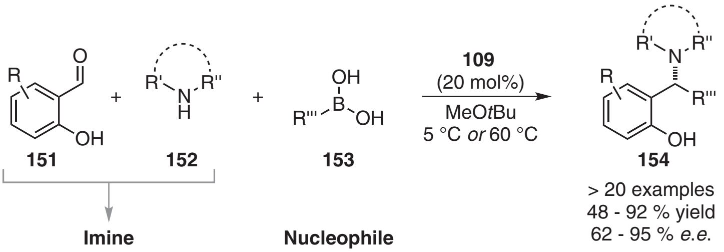
Scheme 42.32 Petasis-type enantioselective vinylation of quinolines using a thiourea catalyst.

Using chiral biphenol catalyst **107**, Lou and Schaus developed a three-component domino Petasis reaction between alkenyl boronates **149**, a wide range of secondary amines **148**, and ethyl glyoxylate (**147**) for the synthesis of chiral α-amino acids **150** (Scheme 42.33) [81].



Scheme 42.33 Enantioselective domino Petasis reaction of ethyl glyoxylates, secondary amines, and various vinyl boronates.

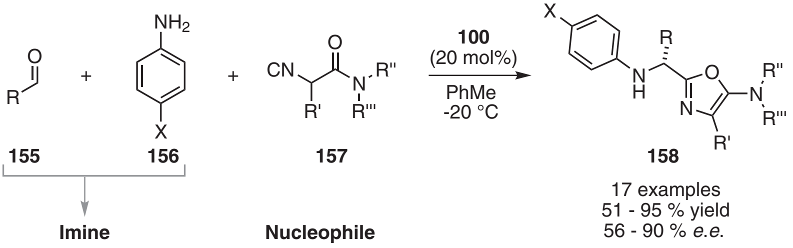
Very recently, the Yuan group combined biphenol **107** and thiourea **112** to give the novel hybrid biphenol-thiourea catalyst **109** (Figure 42.5). This compound catalyzed the domino Petasis coupling of salicaldehydes **151** and cyclic secondary amines **152** employing directly aromatic or vinyl organoboronic acids **153** (instead of their esters) to give various alkylaminophenols **154** (Scheme 42.34) [82].



Scheme 42.34 Enantioselective domino Petasis reaction of salicaldehydes, cyclic secondary amines, and boronic acids using a hybrid biphenol-thiourea catalyst.

42.3.6
Ugi-Type Reaction

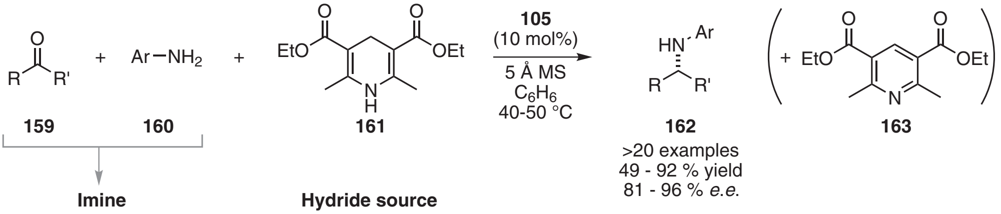
Fifty years ago, Ugi discovered the coupling of a carbonyl compound, an amine, an isocyanide, and a carboxylic acid to give a bis-amide. This is referred to as the Ugi four-component reaction [83]. It has since proven very useful for applications in peptide chemistry and combinatorial synthesis purposes. Despite considerable efforts, however, no general asymmetric four-component Ugi reaction has been developed. This is because the reaction is very fast in the absence of catalysts [84]. As a step towards an enantioselective organocatalyzed Ugi reaction, Wang and Zhu's group reported a related Ugi-type three-component α-addition of isocyanides **157** to *in situ* generated imines catalyzed by the phosphoric acid **100** (Figure 42.5). In this sequential reaction, aldehydes **155** and amines **156** were coupled to form imines before addition of chiral phosphoric acid catalyst **100** and isonitrile **157** (Scheme 42.35). Moderate to good yields and enantioselectivities were achieved for the resulting oxazoles **158.** Importantly, aliphatic aldehydes were also successfully used.



Scheme 42.35 Enantioselective sequential Ugi-type three-component α-addition of isocyanides to imines catalyzed by phosphoric acids.

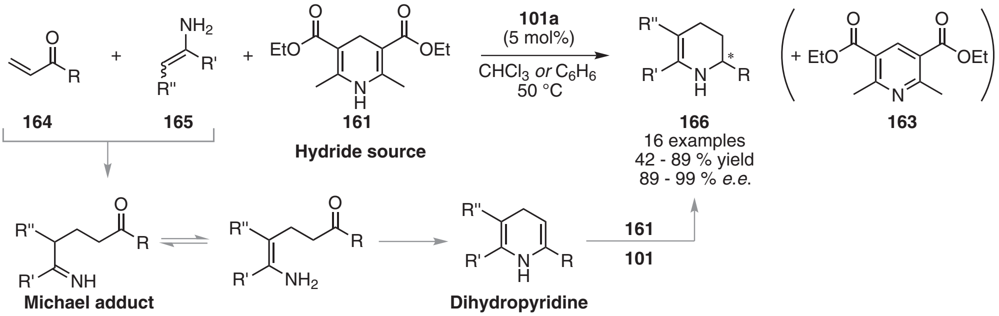
42.3.7
Reductive Amination

Several domino imine formation/reduction sequences have appeared in the literature. However, due to the poor atom economy associated with the employment of the reducing agent (only the hydride of Hantzsch ester **161** is transferred, leaving stoichiometric amounts of pyridine **163** as by-product), their classification as three-component reactions may be regarded borderline. In 2006, MacMillan and coworkers reported the first phosphoric acid-catalyzed enantioselective domino reductive amination of a wide range of ketones **159** using aromatic amines **160** (Scheme 42.36) [85].



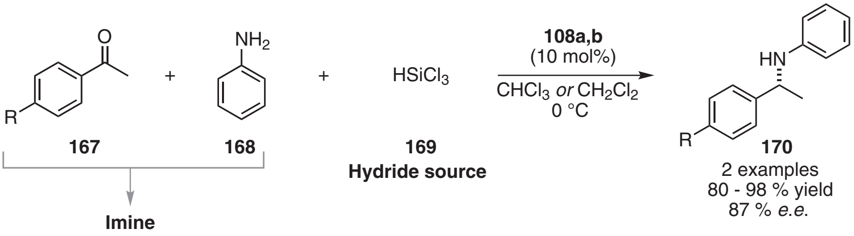
Scheme 42.36 Enantioselective domino reductive amination using the Hantzsch ester as stoichiometric hydride source and catalyzed by a silylated phosphoric acid.

Later, Rueping and Antonchick published a related domino coupling of preformed enamines to conjugated enones in the presence of a Hantzsch ester derivative **161** for subsequent regioselective reduction of the resulting dihydropyridine to tetrahydropyridine **166** (Scheme 42.37). This Michael–cyclization–reduction sequence starting with enone **164** and enamine **165** could be performed in a highly enantioselective manner with moderate to good yields using phosphoric acid **101a** as catalyst (Figure 42.5) [86].



Scheme 42.37 Enantioselective domino phosphoric acid-catalyzed Michael–cyclization–reduction sequence catalyzed by the sterically demanding phosphoric acid **101a** (Figure 42.5).

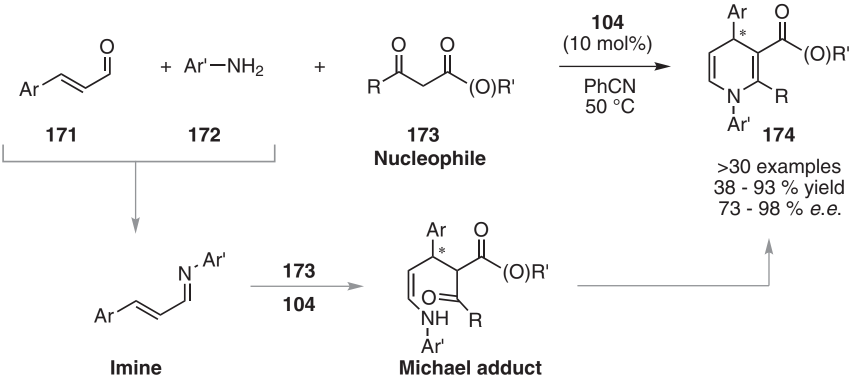
The group of Benaglia reported a sequential reduction of ketimines that worked with trichlorosilane (**169**) as the reducing agent (Scheme 42.38). Furthermore, picolinamides of ephedrine **108a,b** turned out to be viable catalysts for the direct enantioselective reductive amination starting from ketone **167** and aniline (**168**) [87].



Scheme 42.38 Asymmetric sequential reduction of imines with trichlorosilanes catalyzed by ephedrine-based picolinamides.

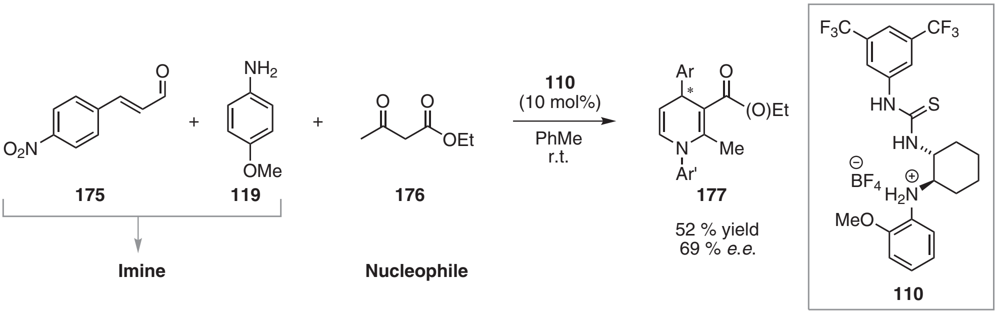
42.3.8
Hantzsch Dihydropyridine and Related Reactions

Dihydropyridine compounds can be conveniently accessed using the Hantzsch multicomponent approach, which was originally developed for the formation of pyridines. A β-ketoester (two equivalents), an aldehyde, and ammonia form a dihydropyridine after Knoevenagel condensation and subsequent Michael addition of an *in situ* formed enamine followed by cyclization [88]. The Gong group disclosed the first catalytic enantioselective sequential Hantzsch-type three-component Michael addition–cyclization sequence affording chiral dihydropyridine compounds. Cinnamaldehyde derivatives **171** and (primary) anilines **172** were used to preform iminium species that were nucleophilically attacked by β-ketoesters **173** (Scheme 42.39). The resulting Michael adduct enamine underwent an intramolecular condensation to give the dihydropyridine products **174** with very good to excellent enantioselectivity when phosphoric acid catalyst **104** was used [89].



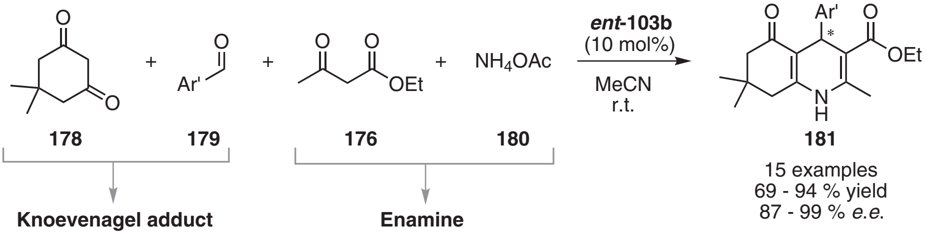
Scheme 42.39 Enantioselective sequential Hantzsch-type reaction of conjugated enals, primary anilines, and 1,3-dicarbonyl compounds catalyzed by sterically demanding phosphoric acids.

Takemoto and colleagues demonstrated that bifunctional ammonium-thiourea catalyst **110**, prepared *in situ* by treatment of a chiral thiourea precatalyst with a strong Brønsted acid, is also able to effect the same sequential transformation enantioselectively (Scheme 42.40). With ee-values of up to 69%, however, the enantiodiscrimination remained comparatively modest [90].



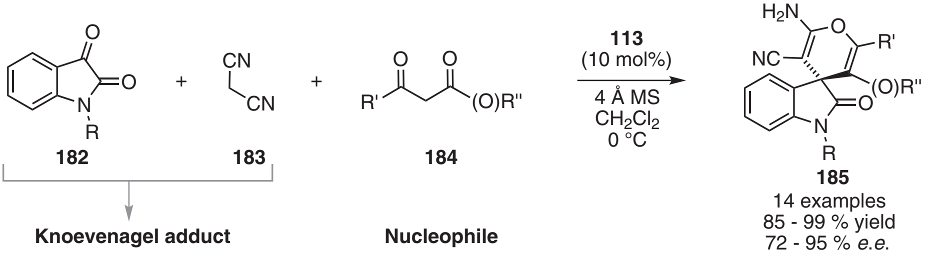
Scheme 42.40 Enantioselective sequential Hantzsch-type synthesis of dihydropyridine **177** starting from *p*-nitrocinnamaldehyde (**175**), anisidine (**119**), and ethyl acetoacetate (**176**). The reaction was catalyzed by a protonated chiral thiourea derivative (**110**): Ar = 4NO$_2$-C$_6$H$_4$; Ar′ = 4MeO-C$_6$H$_4$.

Using chiral phosphoric acid catalysts Evans and Gestwicki expanded the synthetic scope of the Hantzsch reaction. They reported an efficient sequential four-component Hantzsch reaction of dimedone (**178**), aromatic aldehydes **179**, ethyl acetoacetate (**176**), and ammonium acetate (**180**) leading to tetrahydroquinoline products **181** (Scheme 42.41). The use of phosphoric acid catalyst *ent*-**103b** afforded the products in good to excellent yield and enantioselectivity [91].



Scheme 42.41 Enantioselective sequential four-component Hantzsch reaction of dimedone, aromatic aldehydes, ethyl acetoacetate, and ammonium acetate catalyzed by a chiral phosphoric acid.

A three-component reaction related to the Hantzsch-synthesis of dihydropyridines was recently reported by Yuan and colleagues who developed a domino cascade Knoevenagel/Michael/cyclization sequence converting isatin derivatives **182**, malonitrile (**183**), and symmetrical acyclic 1,3-diketones or β-ketoesters **184** into spirocyclic oxindole dihydropyran products (Scheme 42.42). The cinchona alkaloid cupreine (**113**) turned out to be an efficient organocatalyst, delivering dihydropyrans **185** with high yield and enantioselectivity unless cyclic symmetrical 1,3-diketones were used, which gave poor selectivity (<10% ee) [92].

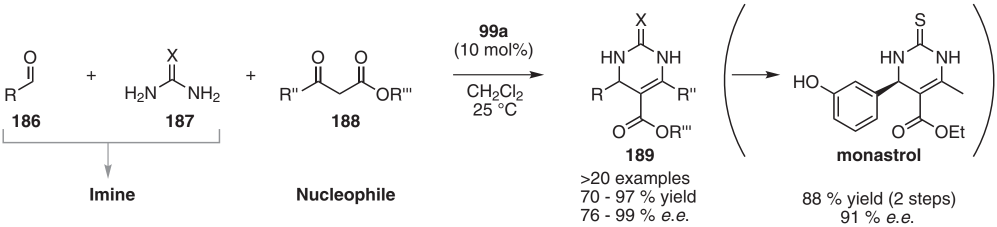


Scheme 42.42 Enantioselective domino Hantzsch-like synthesis of dihydropyrans starting from isatin derivatives, malonitrile, and 1,3-dicarbonyl compounds. The reaction was efficiently catalyzed by cupreine.

Recently, Macaev *et al*. demonstrated that the same reaction can be catalyzed by the related cinchona alkaloids brevicolline, cinchonidine, and cinchonine (up to 94% ee) [93].

42.3.9
Biginelli Reactions

Urea and its derivatives can form imines when treated with aldehydes. In the presence of β-ketoesters, these imines are subject to nucleophilic attack followed by intramolecular imine formation. This three-component transformation is known as the Biginelli reaction [94]. The resulting products are dihydropyrimidinones, which are compounds of high importance in medicinal chemistry [95]. In 2006, Gong and coworkers reported the first organocatalytic Biginelli reactions. Several different aromatic aldehydes **186**, β-ketoesters **188**, and (thio)urea (**187**) were successfully coupled in the presence of chiral phosphoric acid catalyst **99a** (Scheme 42.43). Whereas aromatic aldehydes delivered the desired Biginelli



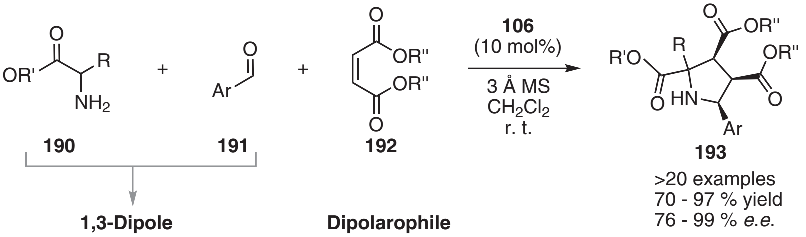
Scheme 42.43 Enantioselective organocatalytic Biginelli reactions, which were included in a synthesis of monastrol.

products **189** with high yield and selectivity (allowing efficient synthetic access to the natural product monastrol), aliphatic aldehydes gave inferior results [96].

The authors further studied variations of the catalysts and found a reversal of enantioselectivity with silyl-substituted catalyst **105** (Figure 42.5), which was rationalized by DFT calculations [97]. The Gong group also found nonlinear effects in certain solvents, indicating that two molecules of the catalyst interact with the substrate [98].

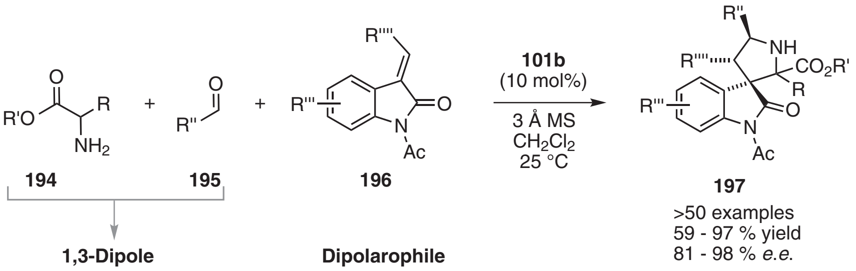
42.3.10
1,3-Dipolar (Huisgen) Cycloaddition Reactions

Cycloaddition reactions of 1,3-dipoles with two-atom dipolarophiles are known as Huisgen cycloadditions [99]. When the 1,3 dipole is formed *in situ*, for example, by condensation of an α-aminocarbonyl compound and an amine, a three-component reaction can be performed in a domino imine formation/cycloaddition fashion. Organocatalytic domino 1,3-dipolar [3+2] cycloadditions were first described by the Gong group. They showed that (aromatic) aldehydes **191** and α-amino-substituted malonates **190** selectively form the corresponding imine dipole that reacts further with electron-deficient olefin dipolarophiles **192** (Scheme 42.44) [100].



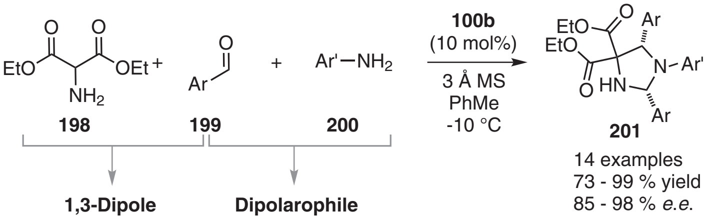
Scheme 42.44 Synthesis of chiral pyrrolidines **193** by enantioselective domino 1,3-dipolar cycloaddition of azomethine ylides formed *in situ* and dialkyl fumarates **192** catalyzed by phosphoric acid catalyst **106**.

Changing the dipolarophile to methylene-indolinones **196** the Gong group also disclosed a domino three-component synthesis of a large collection of medicinally relevant [46] spirooxindoles **197** (Scheme 42.45). The sterically demanding phosphoric acid **101b** was the most effective catalysts for the cycloaddition, affording good to excellent yields and high to excellent enantioselectivity, even when aliphatic aldehydes **195** were used [101].



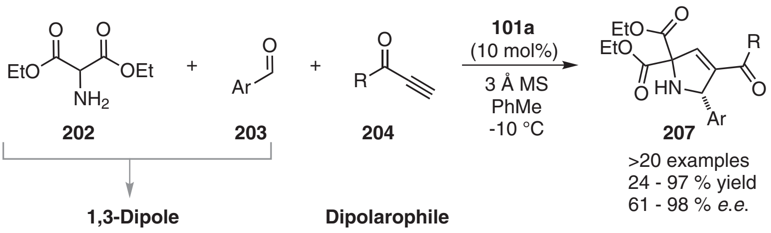
Scheme 42.45 Phosphoric acid-catalyzed enantioselective synthesis of spirooxindoles by enantioselective domino 1,3-dipolar cycloaddition of *in situ* formed azomethine ylides and methylene-indolinones.

The same group reported a chiral Brønsted acid-catalyzed 1,3-dipolar cycloaddition reaction converting aldehydes **199** (2 equivalents), amino esters **198**, and anilines **200** into chiral imidazolidines **201** with high levels of stereoselectivity (up to 82% de and 98% ee, Scheme 42.46). Again, aromatic aldehydes were needed to achieve high enantioselectivity induced by phosphoric acid **100b** [102].



Scheme 42.46 Synthesis of chiral imidazolidines by enantioselective domino 1,3-dipolar cycloaddition of azomethine ylides and imines (both formed *in situ*) catalyzed by phosphoric acid catalyst **100b**.

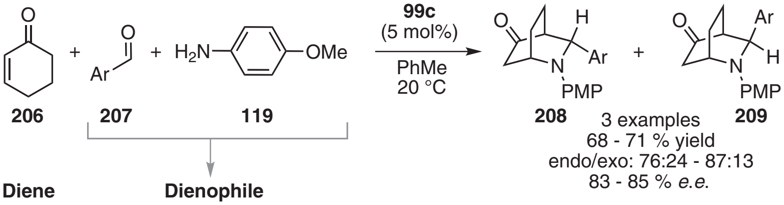
Recently, the Tu group reported the coupling of amino-functionalized malonates **202**, benzaldehydes **203**, and conjugated ynones **204** to furnish 2,5-dihydropyrroles **205** (Scheme 42.47) [103].



Scheme 42.47 Synthesis of dihydropyrroles by 1,3-dipolar cycloaddition using conjugated ynones catalyzed by phosphoric acid catalyst **101a**.

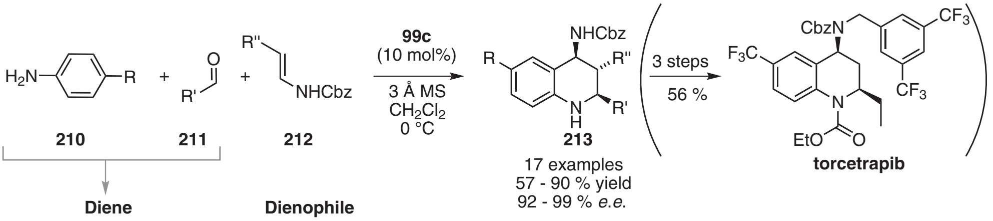
42.3.11
Diels–Alder Reactions

Chiral phosphoric acids also catalyze [4+2] cycloadditions. Gong and colleagues showed that **99c** activates aromatic aldehydes **207**, anisidine (**119**), and cyclohexenone (**206**) to give the *hetero*-Diels–Alder products **208** and **209** with good yield and enantioselectivity, along with moderate *endo*-selectivity (Scheme 42.48) [104].



Scheme 42.48 Chiral phosphoric acid-catalyzed [4+2] cycloaddition of cyclohexenone and aromatic aldimines via three-component methodology.

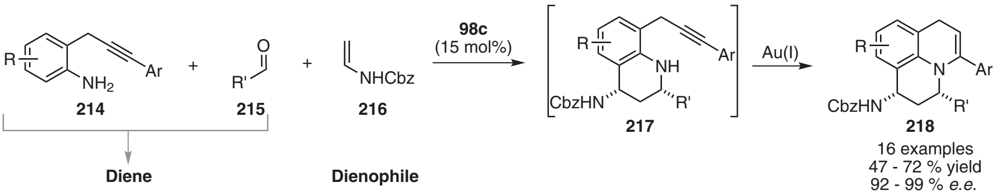
In 2009, Masson, Zhu and coworkers reported a sequential inverse-electron-demand aza-Diels–Alder reaction (Povarov reaction) [105]. They prepared imines *in situ* from the corresponding aldehydes **211** and anilines **210** and reacted them with enecarbamates **212** as electron-rich dienophiles with excellent enantioselectivity using phosphoric acid **99c** (Scheme 42.49). The practicality of their approach was highlighted by its application in an efficient synthesis of the drug torcetrapib [106].



Scheme 42.49 Chiral phosphoric acid-catalyzed Povarov reaction between aromatic aldimines and enecarbamates, affording tetrahydroquinolines **213**.

More recent mechanistic studies performed by the same authors point towards a stepwise cycloaddition mechanism when enecarbamates are used. Furthermore, the catalyst loading could be decreased to very low levels (0.5 mol%) with retention of excellent diastereo- and enantioselectivity [107].

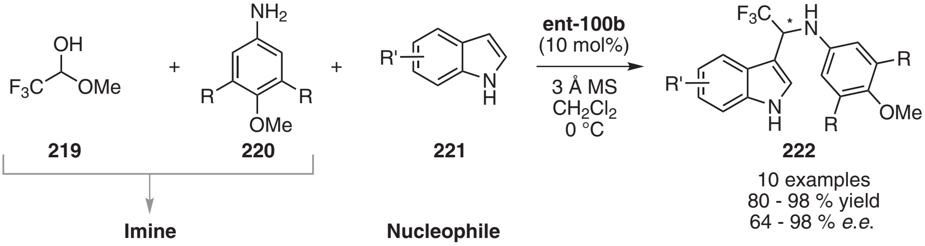
Gong and coworkers coupled an organocatalyzed sequential Povarov reaction, occurring with high yield and enantioselectivity, to a gold-catalyzed intramolecular hydroamination, affording julolidine derivatives **218** (Scheme 42.50). The authors showed that no gold species is involved in the cycloaddition reaction [108].



Scheme 42.50 Sequential asymmetric Povarov reaction between aromatic aldimines (preformed from anilines **214** and aldehydes **215**) and enecarbamates **216** catalyzed by phosphoric acid **98c** followed by an intramolecular gold-catalyzed hydroamination of tetrahydroquinoline intermediate **217**.

42.3.12
Other Reactions

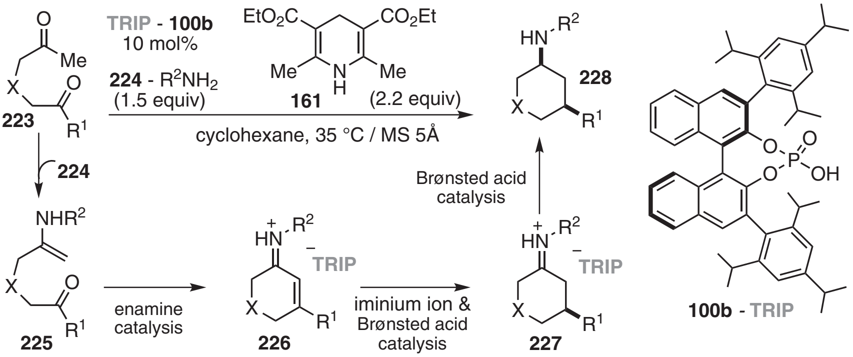
An enantioselective, organocatalytic domino Friedel–Crafts aminoalkylation with imines generated *in situ* from trifluoroacetaldehyde hemiacetal (**219**) and aniline **220** for the synthesis of chiral trifluoromethyl-containing compounds was reported by Ma and coworkers (Scheme 42.51). Very high activity and selectivity was obtained using chiral phosphoric acid catalysts [109].



Scheme 42.51 Asymmetric domino Friedel–Crafts aminoalkylation of imines generated *in situ* from trifluoro-acetaldehyde hemiacetal and anilines catalyzed by a phosphoric acid.

42.4
Merging Covalent and Non-Covalent Activation Modes

As detailed in Sections 42.2 and 42.3, both covalent and non-covalent organocatalytic activation modes have provided efficient strategies to design asymmetric MCRs. A quite recent study by Zhou and List has demonstrated the feasibility of combining asymmetric Brønsted acid catalysis with aminocatalysis to design even more sophisticated reaction sequences toward the synthesis of useful complex molecules. Specifically, they developed a highly enantioselective approach to pharmaceutically relevant 3-substituted cyclohexylamines from 2,6-diketones **223** via an aldolization/dehydration/conjugate reduction/reductive amination domino sequence that is catalyzed by the chiral Brønsted acid **100b** [3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl hydrogen phosphate–TRIP], and accelerated by the achiral amine substrate **224**, which is ultimately incorporated into the product (Scheme 42.52) [110]. In this chemistry, enamine, iminium ion, and Brønsted acid catalysis work in concert in a highly enantioselective and regulated cascade sequence. Central to the successful implementation of the approach is the compatibility of phosphoric acids with the intermediates and products of aminocatalysis.



Scheme 42.52 Combining aminocatalysis and Brønsted acid catalysis to design asymmetric MCRs.

Starting from 2,6-diketones **223** and Hantzsch ester **161**, a combination of a "self-sacrificing" achiral primary amine such as *p*-alkoxy anilines **224** and a catalytic amount of TRIP (**100b**) promotes an aldolization–dehydration step via enamine activation (intermediate **225**). This is followed by an asymmetric conjugate reduction proceeding through the combination of iminium and Brønsted acid catalysis [111] and involving intermediate **226**. The final Brønsted acid-catalyzed reductive amination of **227** affords the corresponding chiral *cis*-3-substituted cyclohexylamines **228**. Interestingly, both the amine and the phosphoric acid are essential for promoting the first two reaction steps, and, among a series of chiral acids tested, only TRIP affords the observed cis-selectivity in the final reductive step.

42.5
Summary and Outlook

Intense investigations into organocatalytic multicomponent domino reactions have led to highly innovative techniques being developed. These techniques are now some of the most reliable and versatile tools for modern asymmetric synthesis. Both covalent and non-covalent modes of catalysis have contributed atom-economical and environmentally benign strategies for rapidly preparing complex chiral molecules with high optical purity. It is expected that the synergistic combination of the two catalytic approaches will likely extend the potential of organocatalytic MCRs to include increasingly daunting synthetic targets, such as the preparation of natural compounds. Given the experimentally simple procedure required, organocatalytic MCRs can become a useful synthetic platform for assembling libraries consisting of enantiopure, stereochemically complex molecules that may increase the probability of success in identifying drug-candidate structures.

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43

Multi-Catalyst Systems

Liwen Xu, Huameng Yang, and Zhihui Shao

43.1

Introduction

Asymmetric catalysis provides a versatile tool for efficiently and selectively making chiral compounds, which is crucial for converting basic chemicals into optically pure products via chirality transfer and amplification [1]. In the past few decades, enantioselective transition metal catalysis has grown into a mature field, and become one of the most useful and powerful tools in organic synthesis [2]. Although the use of small organic molecules as catalysts has been known for more than a century, organocatalysis become a thriving area of widely applicable asymmetric reactions only after the work of Barbas, List, and MacMillan reported in 2000 [3]. Especially in the past golden ten years, asymmetric organocatalysis has attracted considerable attention and played a prominent role in modern organic synthesis [4]. However, the design and synthesis of small molecules that mimic the catalytic activities of enzymes presents a formidable challenge. Inspired by the biomimetic catalysis science at the interface between enzyme catalysis and organocatalysis, the strategy of combinational use of different organocatalysts in certain reactions is very interesting and is being pursued by chemists.

It is almost always the case that the overall increase in reaction rate is greater than that for either catalyst alone when researchers use more than one catalyst to speed up a chemical reaction [5]. As a consequence, much effort has been made in creating designer catalyst systems in the past decade, such as Yamamoto's "designer acids" [6], Shibasaki's bimetallic systems [7], Trost's dizinc complexes [8], and the combinational use of organocatalysts and metal catalysts, and so on [9]. In contrast to these applications of dual catalysis for general organic transformations, the development of multiple organocatalyst cooperative systems for catalytic asymmetric synthesis is still in its infancy. It is only relatively recently that the combinational use of at least two organocatalysts has been recognized as a promising way to overcome synthetic problems related to stereoselectivity and reactivity. This chapter focuses on efforts in the development of multi-organocatalyst, especially dual organocatalyst systems in asymmetric catalysis, which it will discuss with representative examples according to the different

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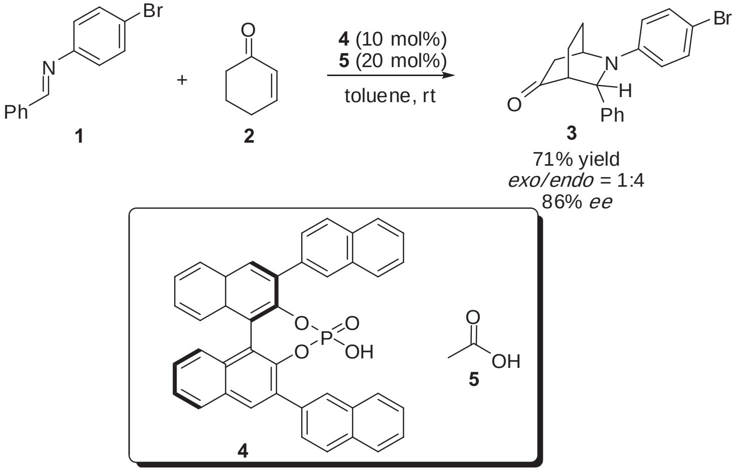
strategies: (i) the combinational use of dual Brønsted acids; (ii) the combinational use of chiral Brønsted acid and chiral or achiral Lewis base, (iii) carbene-based dual organocatalysis, and (iv) amino catalyst-based cooperative catalysis with multifarious co-catalysts.

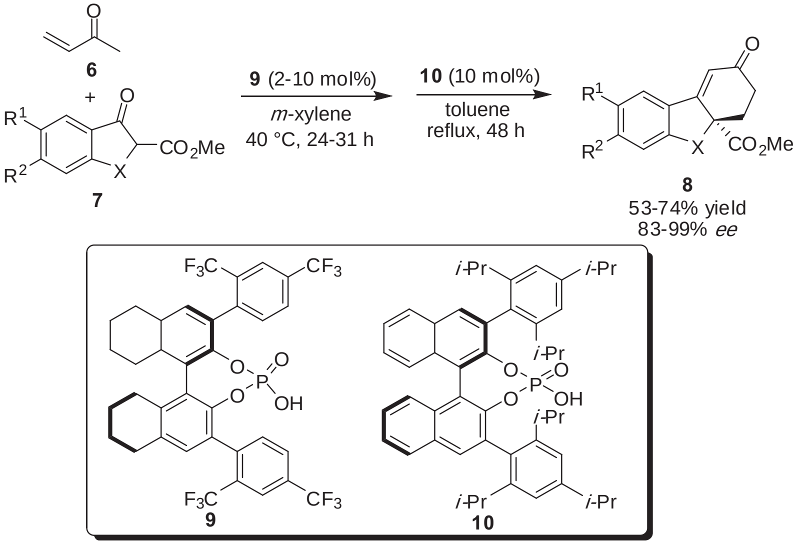
43.2
Combinational Use of Dual Brønsted Acids

The application of chiral Brønsted acids in asymmetric catalysis has increased in recent years [6]. In 2006, Rueping *et al.* reported a double Brønsted acid catalyzed reaction of imine **1** and cyclohexenone **2**, in which the electrophile was activated by a chiral phosphoric acid **4** and the nucleophile was activated by an achiral Brønsted acid **5** (Scheme 43.1) [10]. Various aromatic and heteroaromatic substituted isoquinuclidines with electron-withdrawing and electron-donating substituents could be isolated in good yields and high enantiomeric ratios (82–88% ee), with *exo*/*endo* ratios between 1 : 3 and 1 : 9. The reactivity of a broad range of achiral Brønsted acids was examined and the effect on the enantiomeric induction was obvious (52% ee to 86% ee for the product **3**).



Scheme 43.1 Cooperative Brønsted acid catalyzed synthesis of isoquinuclidines.

The combinational use of two chiral Brønsted acids was also investigated. In 2009, Akiyama and coworkers developed a novel dual catalysis strategy for the enantioselective two-step Robinson-type annulation reaction in the presence of two different chiral Brønsted acid catalysts (Scheme 43.2) [11]. In the first step, a chiral phosphoric acid **9** catalyzed the enantioselective Michael addition reaction of α-alkyl-β-keto esters **7** with methyl vinyl ketone (**6**), and then the Michael products proceeded via a kinetic resolution/intramolecular aldol reaction in the presence of another chiral phosphoric acid (**10**).

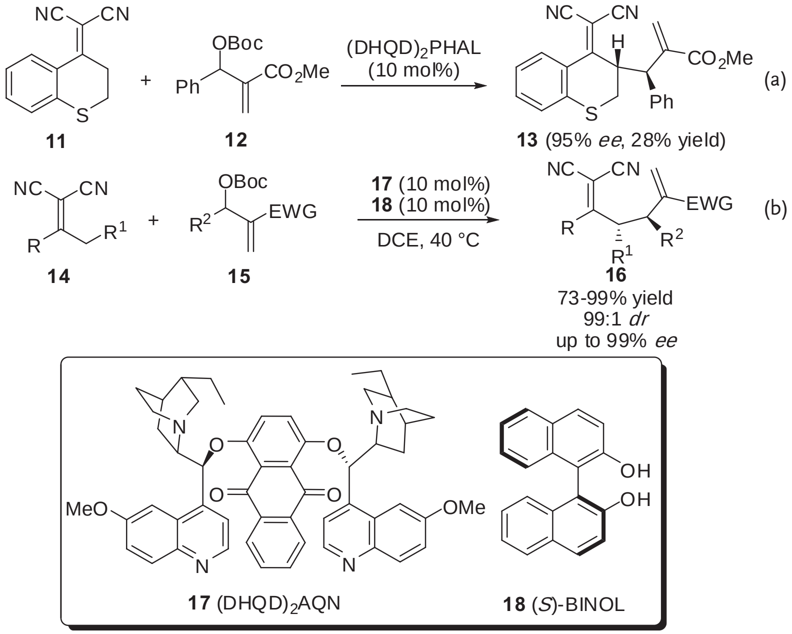


Scheme 43.2 Enantioselective Robinson-type annulation catalyzed by chiral phosphoric acids.

43.3
Combinational Use of Chiral Brønsted Acid and Chiral or Achiral Lewis Base

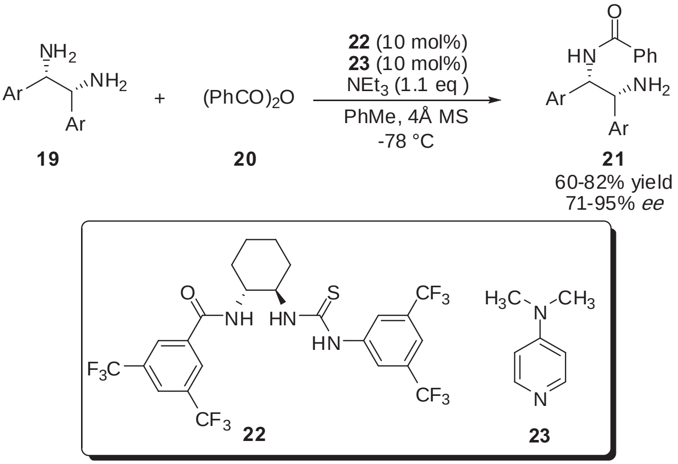
In contrast to the above dual Brønsted acid catalysis, the combinational use of chiral or achiral Lewis base and chiral Brønsted acid proved to be another effective catalyst system. In 2009, Chen and coworkers presented an excellent example in the development of dual organocatalysis with combined chiral Lewis base and chiral Brønsted acid [12]. In their initial study, Chen and coworkers found that cinchona alkaloid-derived Lewis base catalyzed allylic-allylic alkylation of α,α-dicyanoalkenes and Morita–Baylis–Hillman carbonates led to poor enantioselectivities (up to 66% ee). Although the modified cinchona alkaloid [hydroquinidine 1,4-phthalazinediyl diether, $(DHQD)_2PHAL$] showed excellent enantioselectivity (95% ee) in the model reaction (Scheme 43.3a), the reaction was too sluggish (168 h, 28% yield). Interestingly, the utility of (*S*)-BINOL (**18**) as Brønsted acid co-catalyst improved the conversion dramatically. Further screening showed the combinational use of hydroquinidine (anthraquinone-1,4-diyl) diether,

$(DHQD)_2AQN$ (**17**) and **18** resulted in excellent enantioselectivity (95% ee) and isolated yield (97% yield). The scope of the allylic-allylic alkylation of α,α-dicyanoalkenes and Morita–Baylis–Hillman carbonates was explored and excellent results were obtained by the dual catalysis of **17** and **18**. In most cases, excellent stereoselectivities have been achieved for a broad spectrum of substrates (dr > 99 : 1, up to 99% ee).



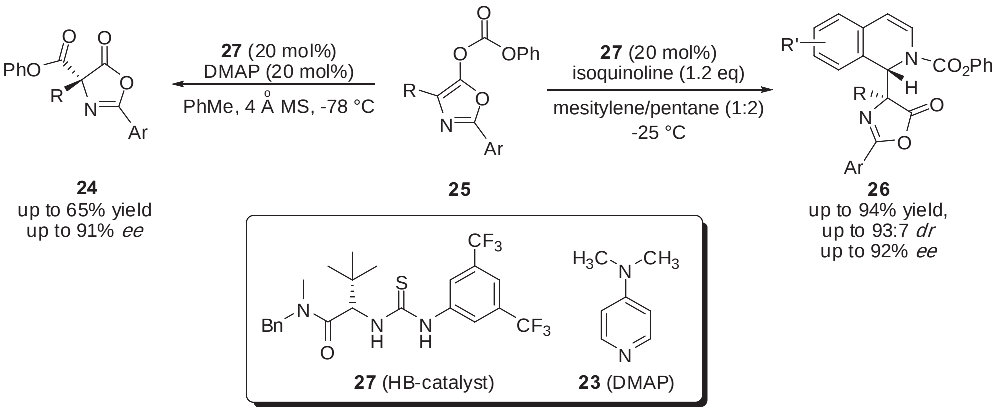
Scheme 43.3 Allylic-allylic alkylation of α,α-dicyanoalkenes and Morita–Baylis–Hillman carbonates by dual organocatalysis.

A simple nucleophilic catalyst such as 4-(dimethylamino)pyridine (DMAP, **23**) has been found to be the ideal catalyst in the kinetic resolution of amines when it was used in combination with a chiral hydrogen-bonding (HB) catalyst [13]. The combined catalyst system formed from DMAP and HB catalyst exhibited excellent enantioselective induction in the kinetic resolution of benzylic [13a], propargylic [13b], and allylic amines [13c] as well as in the desymmetrization of *meso*-1,2-diamines (Scheme 43.4) [13d].



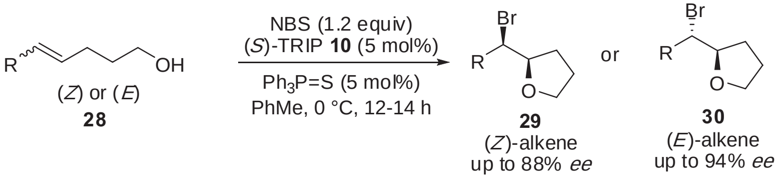
Scheme 43.4 Catalytic enantioselective desymmetrization of *meso*-diamines by merging nucleophilic and HB catalysis.

Recently, a dual organocatalysis approach, namely, the combination of the achiral nucleophilic Lewis base catalyst DMAP (**23**) and the chiral anion-binding thiourea catalyst **27**, was applied to the Steglich rearrangement to provide α,α-disubstituted amino acid derivatives **24** in a highly enantioselective fashion (Scheme 43.5) [14]. Notably, replacement of the nucleophilic co-catalyst DMAP with isoquinoline resulted in an unprecedented transformation that led to α,β-diamino acid derivatives with excellent enantiomeric excesses (88–93% ee).



Scheme 43.5 Dual catalysis approach to the asymmetric Steglich rearrangement.

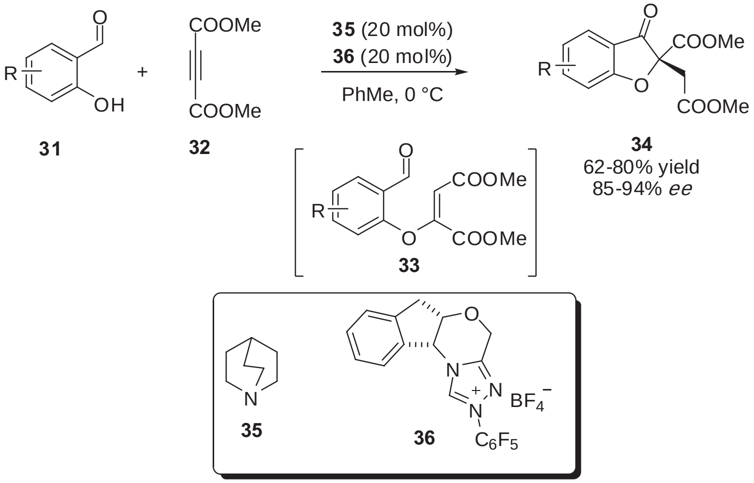
Very recently, a binary catalyst system composed of an achiral Lewis base and a chiral Brønsted acid for the enantioselective bromocycloetherification of 5-arylpentenols **28** was described by Denmark *et al.* (Scheme 43.6) [15]. The combination of the achiral Lewis base $Ph_3P{=}S$ and chiral phosphoric acid **10** afforded good enantioselectivities for the cyclization of (*Z*)-configured 5-arylpentenols to form bromomethyltetrahydrofurans.



Scheme 43.6 Enantioselective bromocycloetherification by Lewis base/chiral Brønsted acid cooperative catalysis.

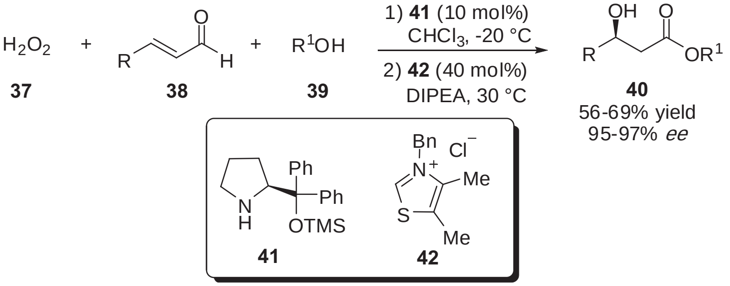
43.4
Carbene-Based Dual Organocatalysis

In a carbene-based multi-catalyst promoted multicomponent reaction, except for the cascade reaction (Scheme 43.7) [16], it is a challenge that each catalyst with different activation modes should be compatible with all reagents, intermediates, and other catalysts present from the onset of the multiple catalyst system for the one-pot domino reaction.



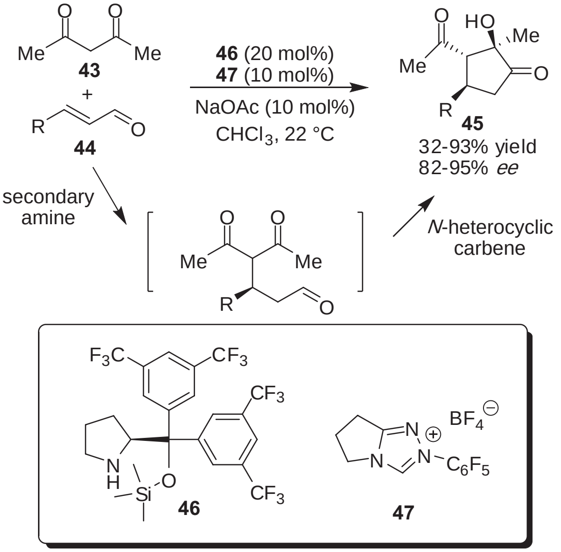
Scheme 43.7 Multi-catalytic asymmetric Michael/Stetter reaction.

In 2007, Córdova and coworker [17] first found that amino and heterocyclic carbene catalysis could be combined in one-pot for the direct catalytic conversion of α,β-unsaturated aldehydes into valuable β-functionalized esters in good to high yields with excellent enantioselectivities (Scheme 43.8). The one-pot combination of chiral amine and heterocyclic carbene catalysis opens up the possibility of biomimetic asymmetric dual organocatalysis based on carbene catalysis.



Scheme 43.8 One-pot combination of amine and heterocyclic carbene catalysis for the synthesis of β-functionalized esters.

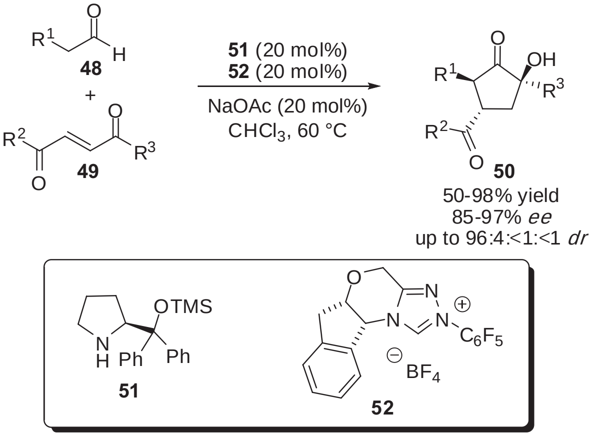
Recently, the catalytic activities of combined amines and N-heterocyclic carbenes (NHCs) have been recognized in various reactions [18]. For example, in 2009, Rovis and coworkers successfully developed a novel one-pot, asymmetric formal [3+2] reaction between 1,3-dicarbonyl compound **43** and α,β-unsaturated aldehydes **44** based on the combinational use of chiral diarylprolinol silyl ether **46** and NHC catalyst **47** (Scheme 43.9) [19]. The dual catalytic process involved a chiral



Scheme 43.9 Secondary amine/N-heterocyclic carbene catalyzed cascade for the synthesis of chiral α-hydroxycyclopentanones.

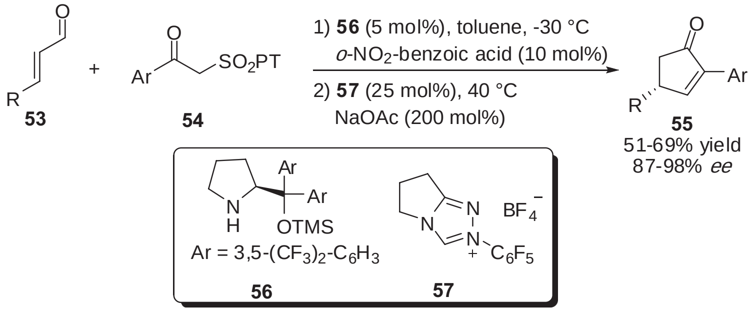
secondary amine catalyzed Michael addition followed by a NHC catalyzed intramolecular crossed benzoin reaction to afford densely functionalized cyclopentanones **45** with high enantioselectivities.

Very recently, Rovis *et al.* [20] reported the application of combined enamine and carbene catalysis in the diastereo- and enantioselective synthesis of functionalized cyclopentanones (Scheme 43.10). The authors proposed that the secondary amine catalyst was capable of epimerizing the α-position of the intermediate aldehyde to form an equilibrium between two diastereomers. Then the chiral triazolium catalyst preferred cyclization with only one of these diastereomers to the final product. The second step of this reaction could be considered analogous to a dynamic kinetic resolution because the Jørgensen–Hayashi amine catalyst would be able to interconvert the two diastereomers.

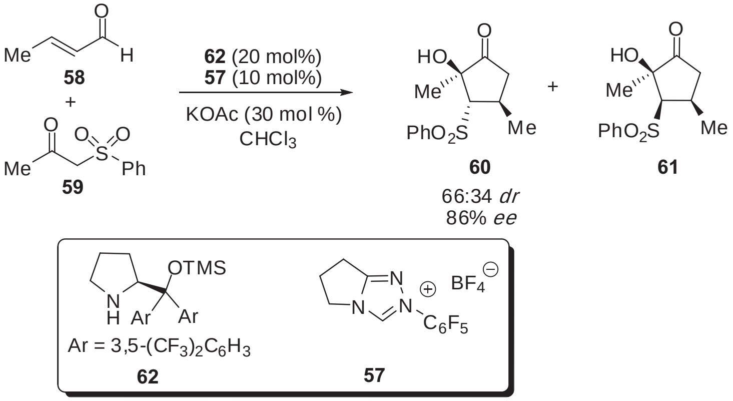


Scheme 43.10 Enamine/carbene cascade catalysis for the synthesis of functionalized cyclopentanones.

With a similar strategy of combined diarylprolinol silyl ether and N-heterocyclic carbene catalysts, Jørgensen and coworkers [21] examined the cascade reaction of easily accessible β-keto heteroaryl-sulfones as nucleophiles with α,β-unsaturated aldehydes (Scheme 43.11). In this cascade reaction, following the initial iminium ion-catalyzed Michael reaction of nucleophiles to α,β-unsaturated aldehydes, the subsequent step was then promoted by carbene catalyst **57** to afford 2,4-disubstituted cyclopentenones **55** via an intramolecular benzoin condensation initiated Smiles rearrangement. The superiority of combinational use of two catalysts in the similar Michael/benzoin cascade reaction was also independently demonstrated by Enders *et al.* (Scheme 43.12) [22].

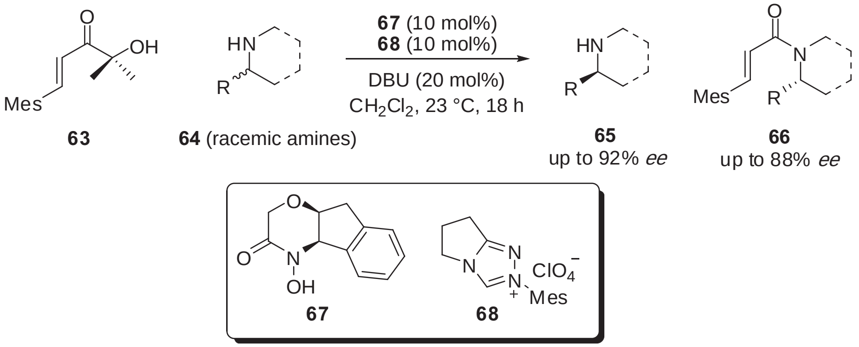


Scheme 43.11 Secondary amine/N-heterocyclic carbene catalysis for the synthesis of 2,4-disubstituted cyclopent-2-enones.



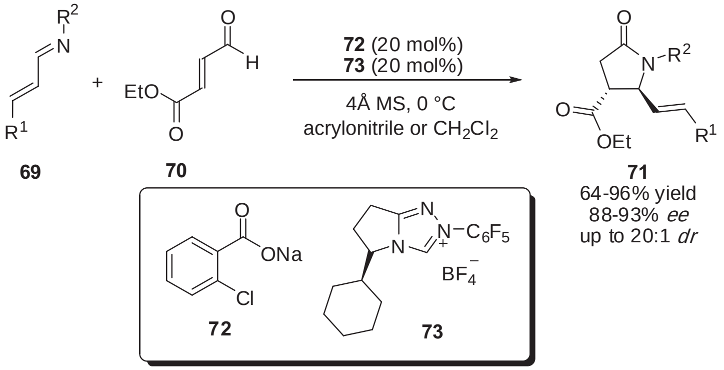
Scheme 43.12 Secondary amine/N-heterocyclic carbene catalysis for the synthesis of functionalized cyclopentanones.

In addition to high background rates and unexpected side-reactions, enantioselective acylations are known to be challenging because the large number of potential transition states leads to unexpected by-products and low enantioselectivities. Based on the findings that the combination of α′-hydroxyenones and amines did not form imines and that the α′-hydroxyenones could be converted into acyl azoliums in the presence of NHCs, Bode *et al.* [23] developed a catalytic kinetic resolution of secondary amines using an achiral NHC working in concert with a chiral acylation co-catalyst (Scheme 43.13). In their report, the *cis*-(1*R*,2*S*)-aminoindanol-derived hydroxamic acid **67** gave excellent results with the aid of the NHC catalyst **68**. This catalytic resolution of secondary amines with α′-hydroxyenones is unique in that two independent catalytic cycles work in concert with complementary reactivity and chemoselectivity, thereby accomplishing an enantioselective reaction that could reach up to 92% ee in good yields.



Scheme 43.13 Catalytic resolution of racemic cyclic amines by merging N-heterocyclic carbene and hydroxamic acid catalysts.

Unlike general NHCs, carbenes derived from the triazolium precatalysts with the *N*-pentafluorophenyl group are far less basic and thus could be compatible with weak acids. On the basis of this observation, Rovis and coworkers [24] have established a novel NHC/Brønsted acid cooperative strategy in the reaction of conjugate imines **69** and ethyl 4-oxobut-2-enoate **70** (Scheme 43.14). The use of the much weaker bases sodium 4-nitrobenzoate and sodium 2-chlorobenzoate (the corresponding conjugate acids: *p*-$NO_2C_6H_4COOH$, pK_a [H_2O] = 3.1; *o*-ClC_6H_4COOH, pK_a [H_2O] = 2.9) afforded the desired products in high yields and good enantioselectivities. With the cooperative N-heterocyclic carbene and Brønsted acid catalysis under optimized conditions, various enals and α,β-unsaturated imines were explored and the corresponding products were obtained in high yields, high enantioselectivities (up to 93% ee), and good diastereoselectivities (>20 : 1 dr).

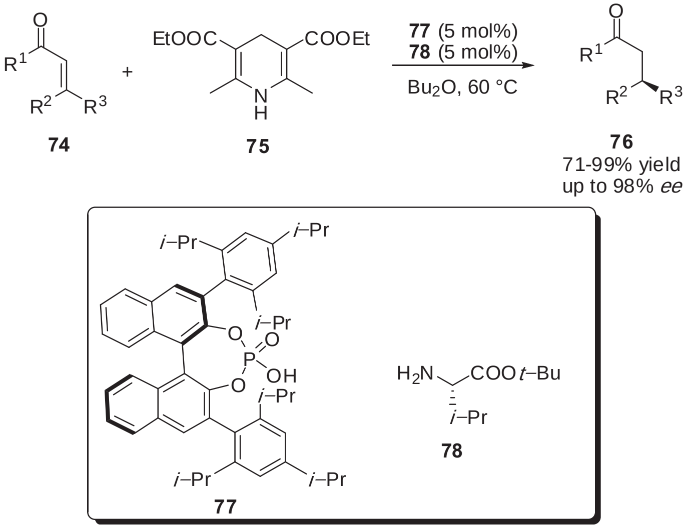


Scheme 43.14 N-heterocyclic carbene and Brønsted acid cooperative catalysis for asymmetric synthesis of *trans*-γ-lactams.

43.5
Amino Catalyst-Based Cooperative Catalysis with Multifarious Co-Catalysts

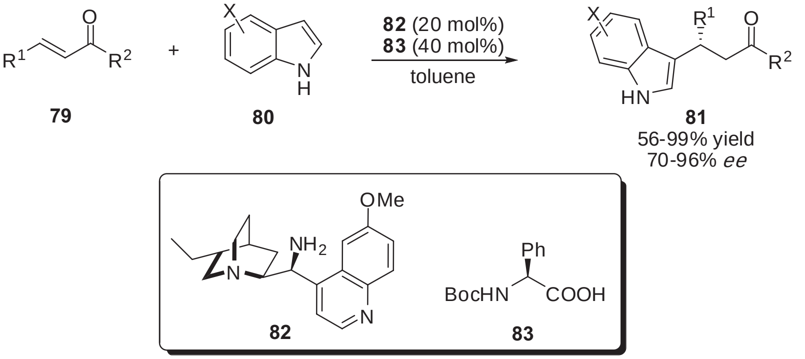
Amino catalysts are one of the most dominant organocatalysts in the activation and transformation of aldehydes or ketones through enamine or iminium intermediates. Initially, the presence of an acid co-catalyst is crucial for the catalytic activation. Later it was realized that the introduction of a chiral counteranion to the catalytic system enables the reactions proceeding through cationic intermediates to be conducted in a highly enantioselective manner, and thus stereochemical control could be effectively induced by the chiral counteranion. This strategy has been defined as asymmetric counterion-directed catalysis (ACDC) [25].

An important early example of the combinational use of a chiral amino catalyst and chiral Brønsted acid was presented by List *et al.* in 2006. They found that the valine ester phosphate salt formed by chiral BINOL-derived Brønsted acid **77** and chiral amino acid-derived primary amine **78** was effective for the transfer hydrogenation of various α,β-unsaturated ketones **74** with commercially available Hantzsch ester **75** to give saturated ketones **76** in excellent enantioselectivities (Scheme 43.15) [26].



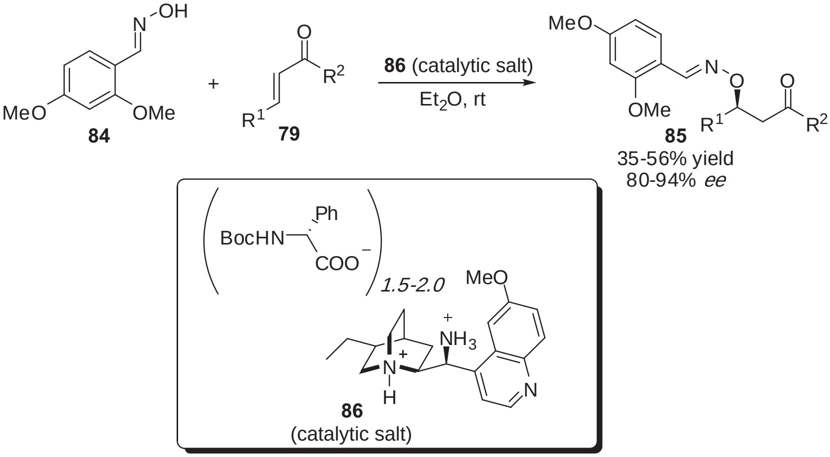
Scheme 43.15 Combining a chiral amino catalyst and a chiral Brønsted acid for the transfer hydrogenation of α,β-unsaturated ketones.

In 2007, Melchiorre and coworkers [27] reported a dual catalyst system based on the combination of chiral primary amine and N-protected amino acid. The combinational chiral counteranion led to the first example of highly enantioselective Friedel–Crafts alkylation of indoles **80** with simple α,β-unsaturated ketones **79** (Scheme 43.16). The N-protected amino acid had a beneficial effect on the stereoselectivity due to the formation of iminium ions of enones imparted by the chiral amino acid.

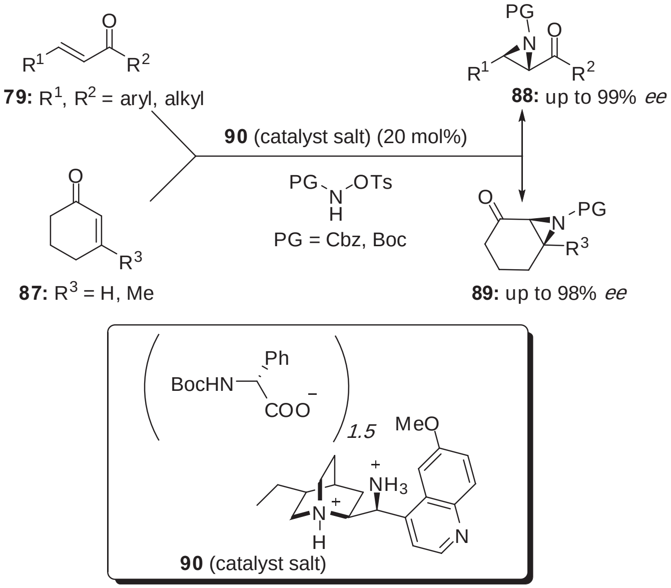


Scheme 43.16 Friedel–Crafts alkylation of indoles with simple α,β-unsaturated ketones by dual catalysis.

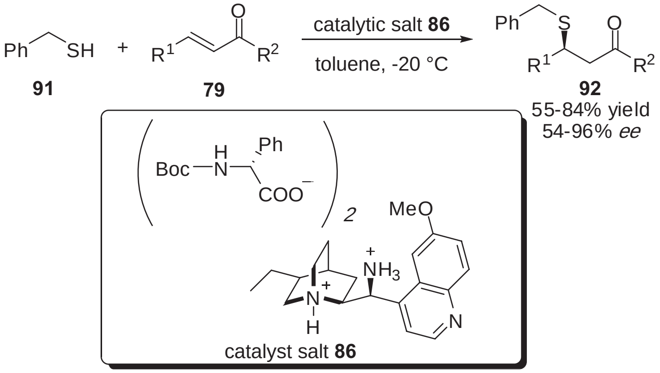
Later, Melchiorre's group employed a similar catalyst system in the β-hydroxylation of α,β-unsaturated ketones **79** (Scheme 43.17) [28], aziridination of enones (Scheme 43.18) [29], and sulfa-Michael addition of α,β-unsaturated ketones (Scheme 43.19) [30]. High chemical yields and excellent enantioselectivities for various chiral products were obtained, which proved the use of chiral co-catalysts to be necessary for optimal enantioselection.



Scheme 43.17 Asymmetric β-hydroxylation of α,β-unsaturated ketones.

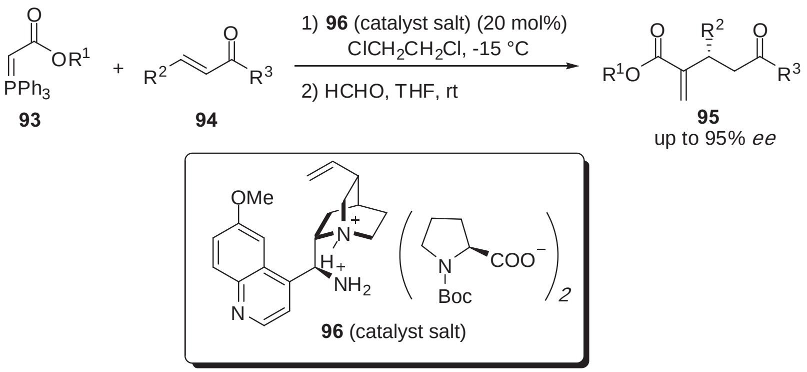


Scheme 43.18 Asymmetric aziridination of α,β-unsaturated ketones.



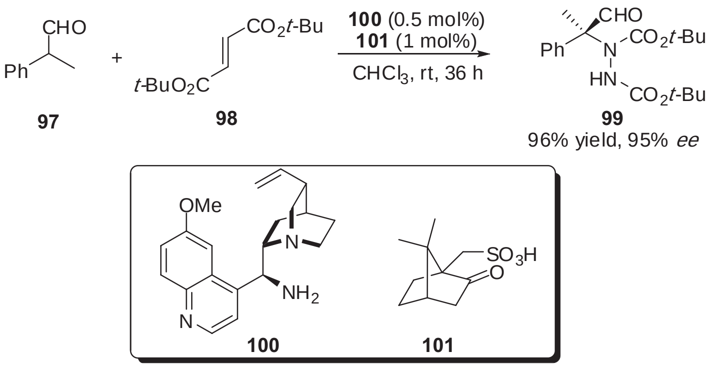
Scheme 43.19 Asymmetric sulfa-Michael addition of α,β-unsaturated ketones.

Very recently, Zhu and Cheng reported an organocatalytic Michael-type addition of phosphorus ylides **93** to α,β-unsaturated ketones **94** using a chiral dual organocatalyst system composed of 9-amino-(9-deoxy)-epi-quinine with Boc-L-proline (Scheme 43.20) [31]. The Michael-type/Wittig reactions proceeded smoothly to provide chiral α-methylene-δ-ketoesters **95** with good to excellent enantioselectivities (up to 95% ee).



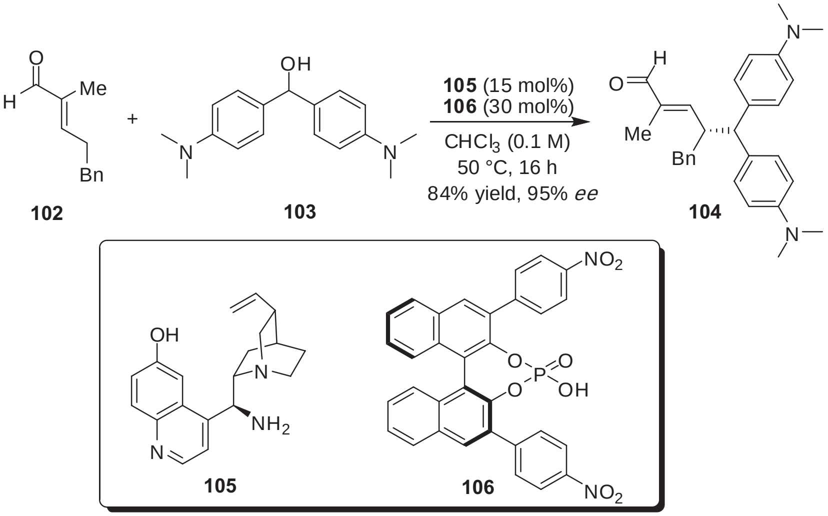
Scheme 43.20 Michael-type addition of phosphorus ylides to α,β-unsaturated ketones using a dual organocatalyst system.

While asymmetric counteranion-directed catalysis (ACDC) has been established as a powerful strategy in iminium catalysis, enamine-based asymmetric counteranion-directed catalysis has not yet been developed. Recently, Lu *et al.* [32] demonstrated that the combination of a cinchona alkaloid-derived primary amine and chiral camphorsulfonic acid (CSA) results in an effective ion-pair catalyst for the directed asymmetric amination of α-branched aldehydes through enamine activation (Scheme 43.21).



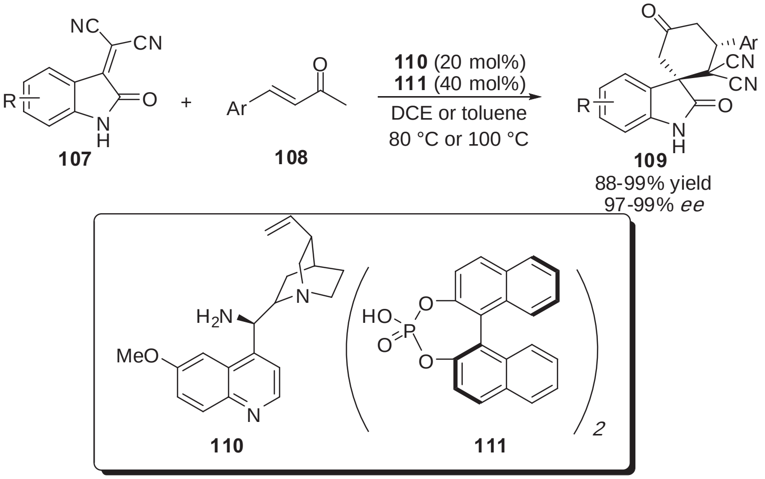
Scheme 43.21 Asymmetric amination of α-branched aldehydes by a primary amine/CSA ion-pair catalyst.

The enantioselective organocatalytic functionalization of carbonyl compounds at the γ position represents a highly challenging and persistent problem for asymmetric synthesis [33]. Recently, Melchiorre and coworkers [34] reported a chiral Brønsted acid-assisted dienamine catalysis for the direct asymmetric γ-alkylation of α-substituted linear α,β-unsaturated aldehydes (Scheme 43.22). In this reaction, the chiral phosphoric acid **106** can induce the formation of a chiral contact ion-pair from alcohol **103** [35], which may synergistically engage in a matched combination with the chiral covalent dienamine intermediate derived from chiral primary amine **105** and α,β-unsaturated aldehyde **102**. The cooperative dual catalysis system afforded the γ-alkylation product **104** with high regio- and enantioselectivities (up to 95% ee).



Scheme 43.22 Cooperative organocatalysis for the asymmetric γ-alkylation of α-branched enals.

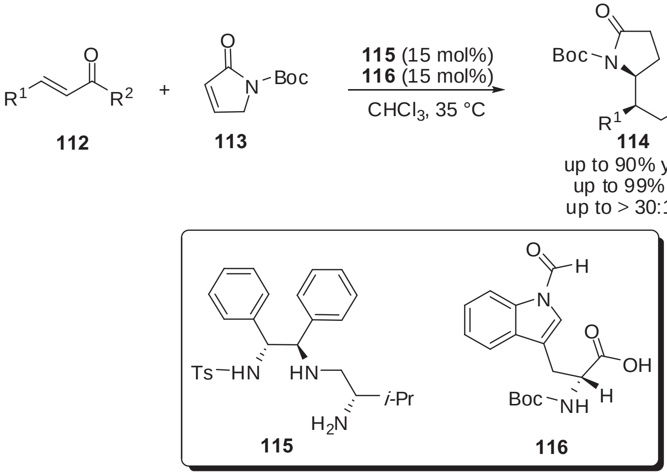
Very recently, the combination of a cinchona-based chiral primary amine and a chiral phosphoric acid has been demonstrated by Wang and coworkers [36] as a powerful and synergistic catalyst system for the double Michael addition of isatylidene malononitriles with α,β-unsaturated ketones (Scheme 43.23). Various novel chiral spiro[cyclohexane-1,3′-indoline]-2′,3-diones were obtained in high



Scheme 43.23 Double Michael addition of isatylidene malononitriles catalyzed by primary amine/phosphoric acid.

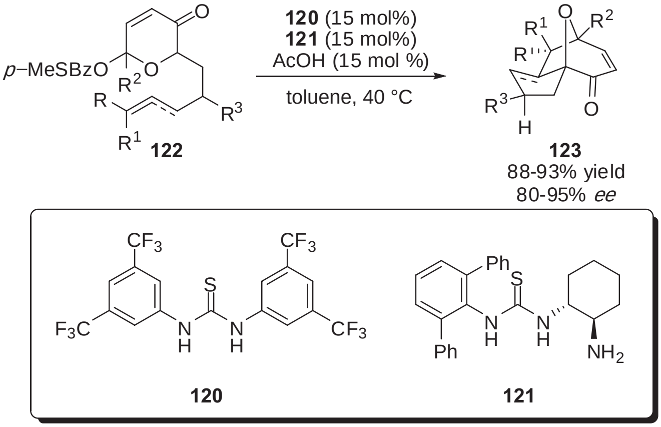
yields (88–99%) with excellent diastereo- and enantioselectivities (94 : 6–99 : 1 dr, 95–99% ee).

The asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam to α,β-unsaturated ketones is a challenging task regarding the reactivity and stereoselectivity. Recently, Ye *et al.* [37]. achieved this asymmetric transformation with a multifunctional catalytic system. A series of primary amine catalysts were screened in initial experiments; however, the conversion and diastereoselectivity were disappointing. Interestingly, the excellent enantio- and diastereoselectivity [98% ee, 15 : 1 dr, and 98% yield, for (*E*)-4-phenylbut-3-en-2-one] could be obtained using the dual catalytic system consisting of **115** and N-Boc-L-Trp **116**. Notably, this well-established dual organocatalysis approach could be utilized for a large variety of α,β-unsaturated ketones bearing either electron-donating or electron-withdrawing groups (Scheme 43.24). The corresponding Michael products could be acquired in excellent yields (75–90%) with excellent enantio- (95–99% ee) and diastereoselectivity (4 : 1–30 : 1 dr).



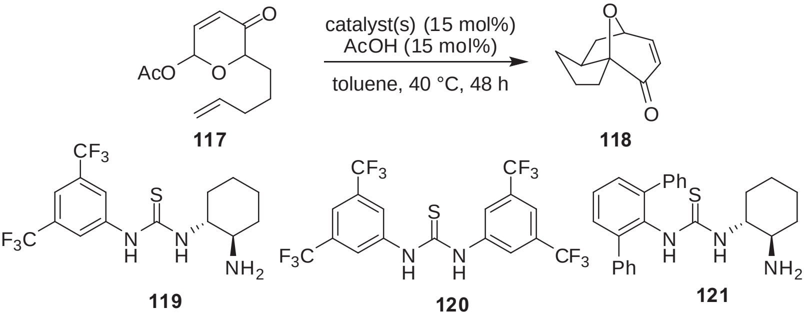
Scheme 43.24 Direct vinylogous Michael addition under multifunctional catalysis.

In 2011, Jacobsen *et al.* [38] reported a dual catalyst system consisting of a chiral primary amine thiourea and an achiral thiourea that promoted an intramolecular variant of the oxidopyrylium-based [5+2] cycloaddition reaction with high enantioselectivity (Scheme 43.25). Initially, poor enantioselectivity (21% ee) was obtained in the presence of catalyst **119**. Subsequent studies showed that the addition of an achiral thiourea catalyst **120** dramatically improved the reaction enantioselectivity (67% ee, entry 2, Table 43.1). Further optimization led to the identification of **121**, which bears a 2,6-diphenylanilide component, as the most enantioselective aminothiourea catalyst (88% ee, entry 3, Table 43.1). A clear and dramatic cooperative effect between the optimal catalysts was supported by a series of experiments. With optimal catalytic conditions, valuable tricyclic structures were obtained in moderate to good yields and with high enantioselectivities (up to 95% ee) (Scheme 43.25).



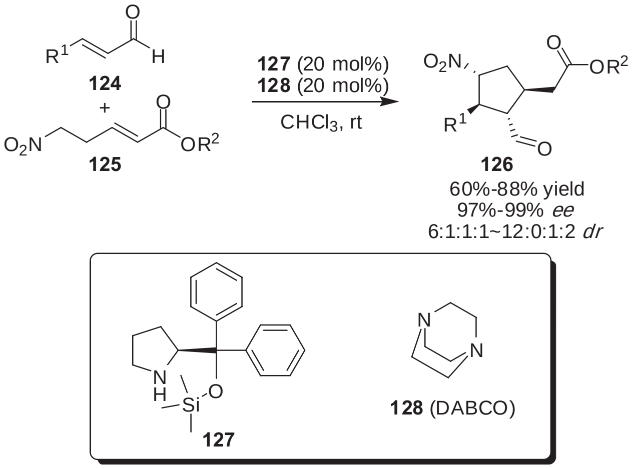
Scheme 43.25 Enantioselective oxidopyrylium-based [5+2] cycloadditions by dual catalysis.

Table 43.1 Representative examples in the search for dual organocatalyst systems.



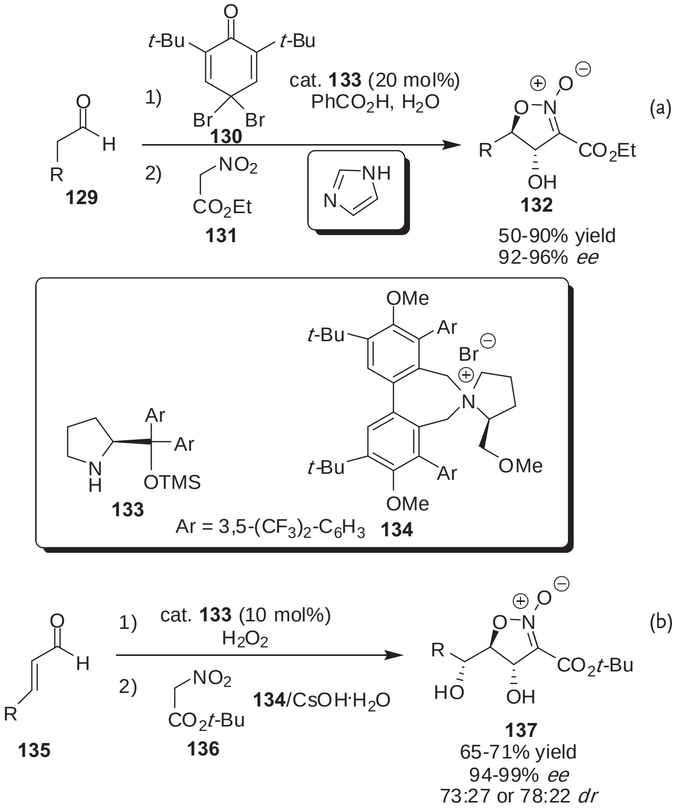
Entry	Catalyst(s)	Yield (%)	ee (%)
1	**119**	37	21
2	**119** + **120**	53	67
3	**120** + **121**	30	88

Chiral secondary amines are another important class of privileged functional component in dual organocatalysis that has been widely used in asymmetric catalysis [39]. For example, in 2008, Córdova *et al.* [40] reported the combinational use of (*S*)-diphenylprolinol TMS ether (**127**) and Brønsted base DABCO (**128**) as dual organocatalysts to promote the asymmetric domino double Michael addition reaction (nitro-Michael/Michael reaction) of 5-nitropentenoate (**125**) to α,β-unsaturated aldehydes (Scheme 43.26), which gave the corresponding nitrogen-, formyl-, and ester-functionalized cyclopentene derivatives **126** with four stereocenters (97–99% ee).



Scheme 43.26 Asymmetric domino double Michael addition catalyzed by chiral secondary amine/achiral Brønsted base.

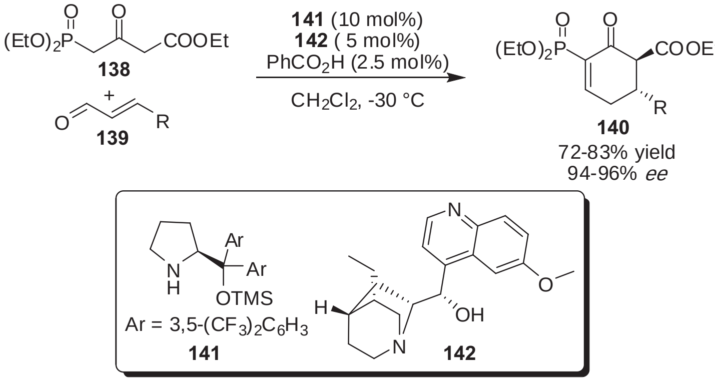
In this context, Jørgensen and coworkers [41] reported a new enantio- and diastereoselective domino α-bromination/Henry/O-alkylation cyclization sequence to access 4,5-disubstituted isoxazoline *N*-oxides, as well as demonstrating the use of this domino protocol for the *de novo* synthesis of β,γ-dihydroxylated and β,γ,δ-trihydroxylated α-amino acids derivatives, phytosphingosines, and amino sugars. In this domino reaction, the chirality stored within the α-carbonyl sp^3-carbon center, formed by the direct α-bromination of aldehydes by the electrophilic bromination reagent catalyzed by the TMS-protected diaryl-prolinol **133**, is fully exploited by a base-promoted face-selective Henry addition of nitroacetates and subsequent stereospecific O-alkylation, furnishing the enantio- and diastereoselective synthesis of 4,5-disubstituted isoxazoline *N*-oxides in one pot (Scheme 43.27a). Jørgensen and coworkers also expanded this strategy to the creation of one additional stereocenter. This approach utilizes the organocatalytic epoxidation of α,β-unsaturated aldehydes **135** by hydrogen peroxide and TMS-protected diarylprolinol **133** as the catalyst. A thorough screening of diverse chiral and non-chiral bases and hydrogen-bonding catalysts favored the use of solid CsOH as the base in the presence of a chiral phase-transfer catalyst, the Lygo-type chiral ammonium salt **134**. The aromatic, aliphatic, and functionalized α,β-unsaturated aldehydes all participated in the desired reactions to provide the enantiopure products in moderate to good yields and diastereoselectivities (Scheme 43.27b).



Scheme 43.27 Asymmetric synthesis of 4,5-disubstituted isoxazoline *N*-oxides promoted by a multi-catalyst system.

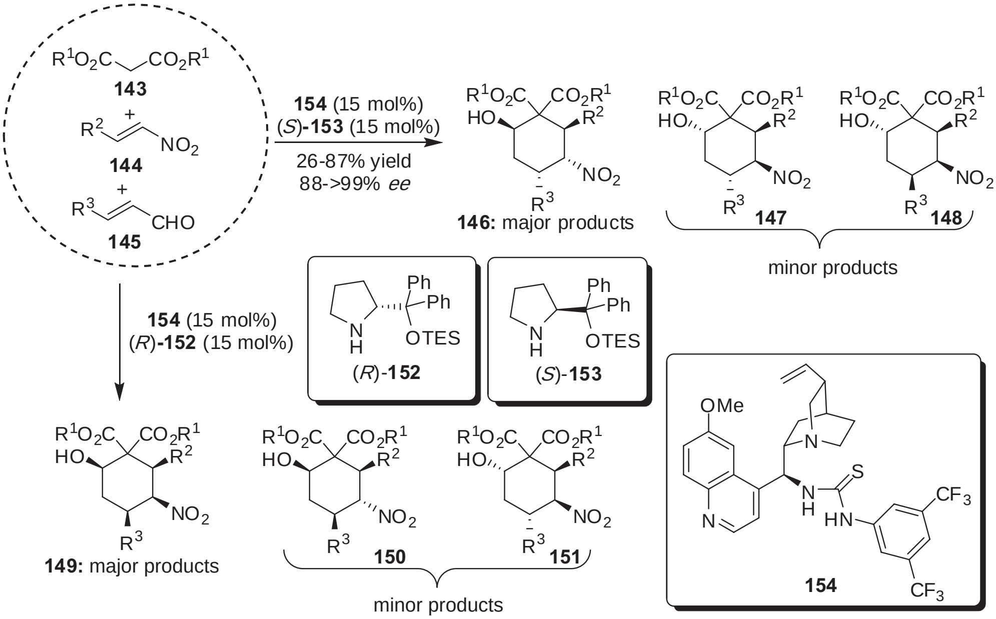
During their studies on the chiral diarylprolinol silyl ether-catalyzed domino Michael–Knoevenagel condensation reaction of α,β-unsaturated aldehydes **139** and ethyl 4-diethoxyphosphoryl-3-oxobutanoate (**138**), Jørgensen and coworkers found aliphatic enals were unreactive in the presence of the chiral secondary amine catalyst [42]. A further screening of different additives or co-catalysts revealed that the use of an additional basic co-catalyst was crucial for the reaction to proceed in high enantioselectivities and yields (Scheme 43.28). Interestingly, the presence of the chiral hydroquinine (DHQ) **142** had no major impact on the stereochemical outcome of the reaction, indicating that no matching–mismatching interaction between catalyst and co-catalyst occurred, which proved that hydroquinine **142** worked as a base to facilitate formation of the corresponding enol of ethyl 4-diethoxyphosphoryl-3-oxobutanoate, and chiral diarylprolinol silyl ether **141** activated α,β-unsaturated aldehydes with iminium catalysis.

In 2009, Xu and Dixon reported an elegant example of dual catalyst controlled stereoisomer selection in the synthesis of functionalized cyclohexanes [43]. In their



Scheme 43.28 Secondary amine/DHQ catalyzed Michael–Knoevenagel condensation of aliphatic enals.

hypothesis, a bifunctional base/Brønsted acid catalyst preferentially activates the malonate esters **143** and the nitroalkenes **144**, thus firstly promoting a chemoselective and stereoselective Michael addition. The Michael adducts then serve as the donors in a regioselective nitro-Michael reaction with α,β-unsaturated aldehydes **145** under iminium ion activation with diarylprolinol silyl ether. In this relay cascade reaction, two different catalysts have different roles and there are putative matched and mismatched combinations of reaction intermediates and catalyst pairs. As shown in Scheme 43.29 and Table 43.2, the triple cascade



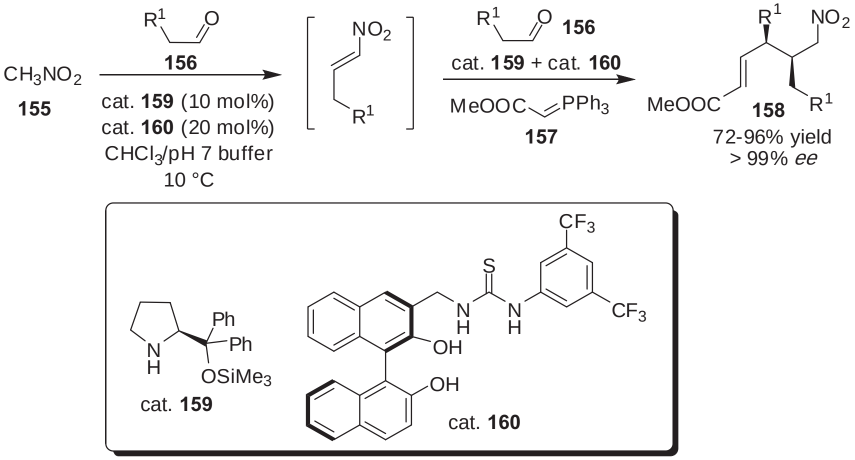
Scheme 43.29 Dual catalyst promoted relay cascade for the synthesis of functionalized cyclohexanes.

Table 43.2 Representative examples of the dual catalyst promoted cascade reaction (Scheme 43.29).

Entry	R^1	R^2	R^3	Yield (%)	dr	ee (%)
1	Me	2-BrC_6H_4	Ph	63	64:20:16	98
2	Me	4-$CH_3C_6H_4$	Ph	61	68:16:16	>99
3	Me	4-ClC_6H_4	Ph	52	64:24:12	>99
4	Me	Ph	2-$CH_3C_6H_4$	45	64:21:16	>99
5	Me	Ph	4-CNC_6H_4	67	48:35:17	>99
6	Me	2-Furyl	4-CNC_6H_4	74	84:16:9	>99
7	Et	2-BrC_6H_4	Ph	56	61:20:20	>99

reaction worked efficiently, affording high selectivities (up to 99% ee for major isomers).

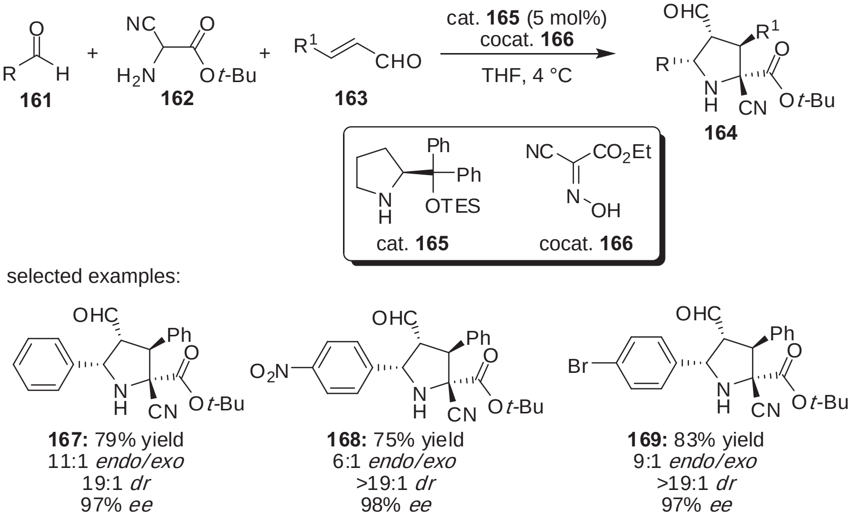
The nitro group enjoys a privileged position that could be activated by hydrogen-bond catalysis, and the aldehyde moiety can react with a secondary amine to form an enamine intermediate that promotes the α-functionalization of aldehydes. Based on this hypothesis, Pihko and coworkers [44] designed a novel three-component domino reaction with nitromethane, alkyl aldehydes, and a phosphorane through the combinational use of hydrogen-bond and enamine catalysis. In the absence of chiral Brønsted acid, the domino reaction gave almost no desired products; the types of Brønsted acids are also crucial for the enantioselective three-component domino reaction. As shown in Scheme 43.30, there are two step reactions promoted by dual organocatalysts with cooperative catalysis: (i) step 1, the condensation of aldehydes **156** with nitromethane (**155**) yielded nitroolefins and (ii) step 2 the asymmetric Michael addition of aldehydes to nitroolefins readily



Scheme 43.30 Dual hydrogen-bond/enamine catalyzed enantioselective aldehyde–nitroalkene–aldehyde domino reaction.

happened in the presence of chiral Brønsted acid **160** and diarylprolinol silyl ether **159**, thus providing the products in excellent diastereo- and enantioselectivities.

Although the nitro moiety exhibits promising reactivity in the presence of chiral Brønsted acids because of hydrogen-bond activation, the carbonyl or imine group has a stronger hydrogen-bond-acceptor capacity than the nitro group [45]. Very recently, Córdova *et al.* [46] demonstrated that the reaction of aldehydes and protected α-cyanoglycine esters could be pushed towards imine formation and subsequent [2+3] cycloaddition with enals by adding a hydrogen-bond donating co-catalyst to the dynamic three-component system. In their initial studies – no co-catalyst but only the chiral diarylprolinol silyl ether as enamine catalyst – the three-component reaction gave predominantly the Michael adduct and a small amount (15% yield) of desired polysubstituted chiral pyrrolidine in moderate enantioselectivity (73% ee). Extensive screening of co-catalysts showed that the hydrogen-bond-donating compound **166** promoted the three-component reaction and dramatically improved the reaction rate and enantioselectivity. As shown in Scheme 43.31, the dual organo-co-catalytic asymmetric three-component reactions of aldehydes **161**, protected α-cyanoglycine **162**, and α,β-unsaturated ketones **163** gave the corresponding highly substituted α-quaternary proline derivatives as the predominant diastereoisomers in good to high yields.



Scheme 43.31 Dynamic three-component asymmetric transformation by the combination of hydrogen-bond-donating and amine catalysts.

43.6
Conclusions

Although examples of synergistic organocatalysis or multiple organocatalysts, especially dual organocatalyst systems, have been reported in recent years the development of multiple organocatalysts for new reactions is still in its infancy and is fascinating since it has enabled unprecedented or non-selective transformations to become highly reactive and stereoselective. As can be seen from the research results reported, moving from a single organocatalyst to multifunctional synergistic organocatalysis has proved to be an effective strategy in new reaction development. Undoubtedly, the future direction is to continue to expand the scope of multi-organocatalyst systems with unique catalytic features through the matching of different chiral catalysts.

Acknowledgments

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44
Organocatalysis in Total Synthesis

Eugenia Marqués-López and Raquel P. Herrera

44.1
Introduction

There is no doubt about the importance of natural products in chemistry, biology, and medicine and, consequently, their obtainment has always been a theme of interest for chemists. This traditionally centered on their direct extraction from natural sources, while later the value of natural product synthesis has become unquestioned. Usually, these compounds present stereogenic carbon centers and, therefore, their syntheses must involve ways of obtaining chirality. The chiral pool and resolution of racemates represented the two principal strategies until the birth of asymmetric catalysis [1], which has revolutionized chemical synthesis. In this context, asymmetric organocatalysis [2] appeared in the first decade of twenty-first century as a promising powerful tool, complementing metal and enzymatic catalysis. Since seminal works [3], this field has grown exponentially due to its main advantage: simplicity. In addition, although the synthesis of complex molecules is still an active challenge in organocatalysis, there are already a large number of those syntheses where organocatalyzed reactions play a crucial role, showing its efficiency with elegance. In this recapitulation we will describe several selected examples published in recent years [4]. Moreover, this chapter is divided into different sections according to the most important modes of activation, such as enamine and iminium catalysis, Brønsted acid and hydrogen bond catalysis, cinchona alkaloid catalysis, and phase-transfer catalysis.

44.2
Aminocatalysis in Natural Product Synthesis

Within organocatalysis, aminocatalysis has represented a key approach in a high variety of fundamental transformations [5]. Since the pioneering works reported contemporaneously by List [3a] and MacMillan [3b] in 2000, numerous outcomes have been the achieved in this appealing area. In the last 12 years many research

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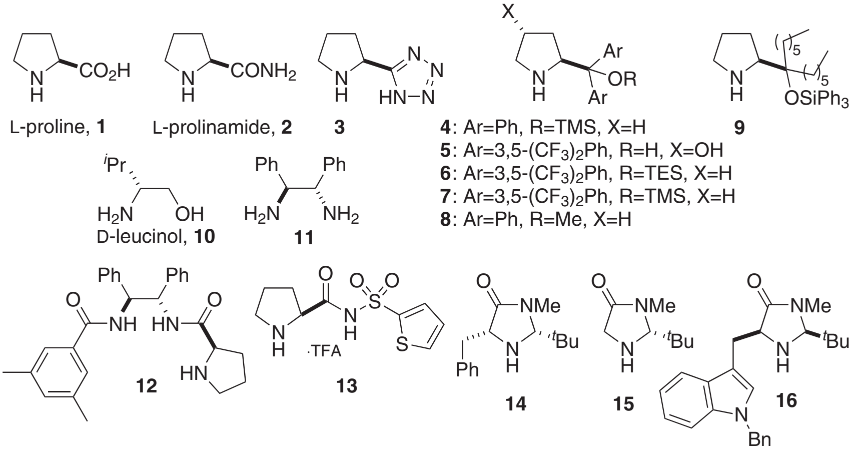


Figure 44.1 Chiral amines used as organocatalysts in natural product synthesis.

groups have used secondary and, more recently, primary chiral amines, which have become privileged structures as organocatalysts (Figure 44.1).

44.2.1
Enamine Catalysis

The condensation reaction between an amine and an enolizable carbonyl compound rapidly affords reactive enamines as nucleophilic intermediates, which have the capacity to react with an extensive range of electrophiles, rendering the corresponding α-functionalization of those carbonyl compounds [6]. Since the pioneering work reported by List *et al.* [3a], in the last decade this mode of activation has witnessed explosive growth in the field of organocatalysis. It is easy to find many examples in the literature of the application in total synthesis of this catalysis through different reactions (Figure 44.2). One of the most extensively explored has been the aldol reaction, a key step in the syntheses of callipeltoside C [7], convolutamydine A, B, and E [8], (+)-przewalskin B [9], (−)-salinosporamide A [10], (+)-spongistatin 1 [11], (*S*)-(−)-3-butylphthalide [12], and (−)-anominine [13] among many other examples. The Mannich reaction, a classical method for the creation of new C–C bonds, can be found in the synthesis of natural products such as (2*S*,3*R*,4*S*)-4-hydroxyisoleucine [14]. Furthermore, α-heterofunctionalization of carbonyl compounds via enamine activation has also been applied in the synthesis of natural products. Among other examples, α-oxidation is the most frequent – 7,8-*O*-isopropylidene iriomoteolide-3a [15], (+)-neosymbioimine [16], (+)- and (−)-disparlure [17], (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide [18], and Hagen's gland lactones [19] – followed by α-amination: chloptosin [20], (*S*)-AIDA [21], and *Lycopodium* alkaloids [22]. Sometimes α-heterofunctionalization of carbonyl compounds is necessary to form a temporal reactive intermediate, as is the case of

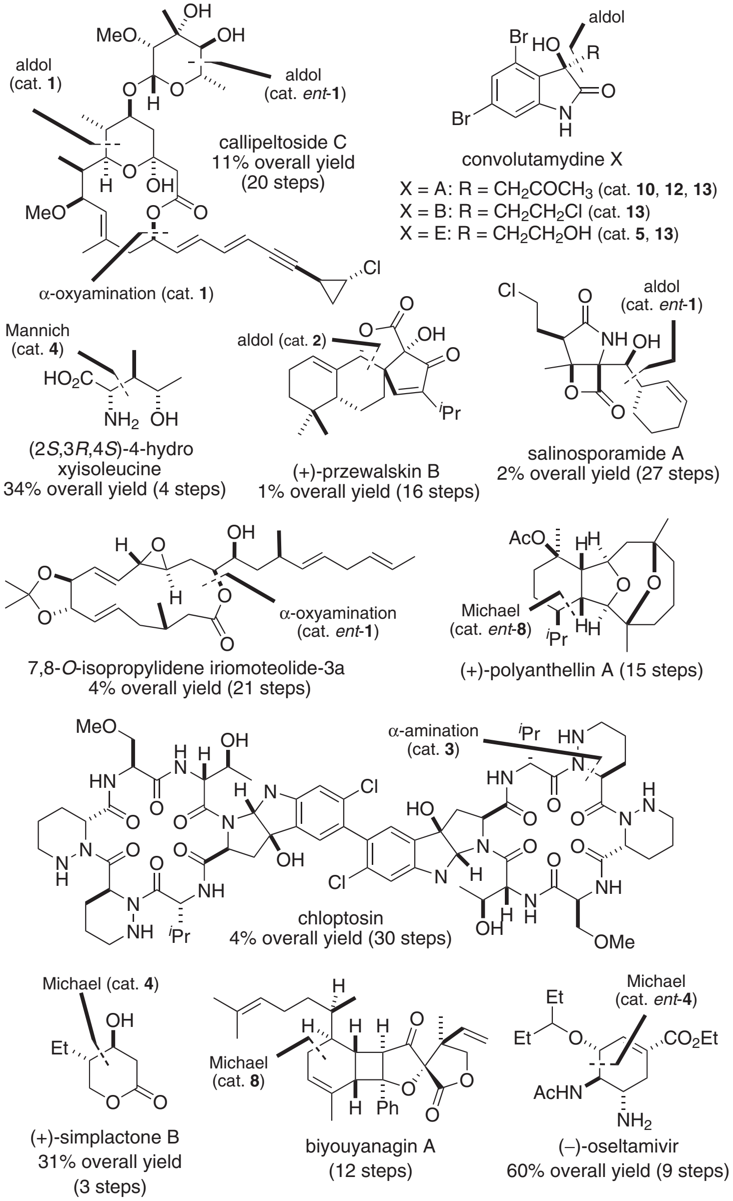
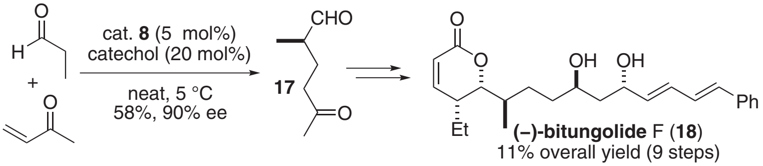


Figure 44.2 α-Functionalization of carbonyl compounds via enamine catalysis applied in total synthesis.

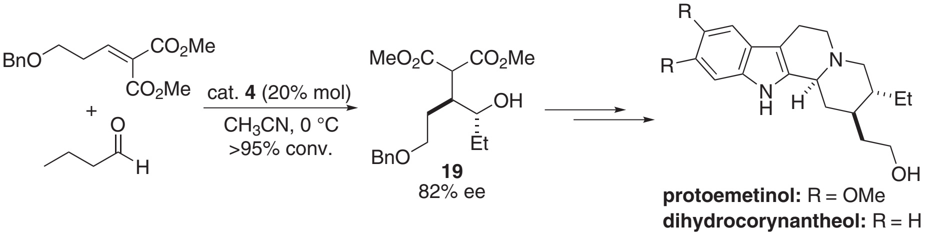
α-selenylation: (+)-symbioramide [23], and α-chlorination: ripostatin B [24]. Moreover, the organocatalytic Michael addition is another main C–C bond-forming strategy widely used in natural product synthesis. Illustrative examples are the syntheses of (+)-polyanthellin A [25], (+)-simplactone B [26], biyouyanagin A [27], (−)-oseltamivir [28, 29], and ABT-341 [29, 30] (Figure 44.2).

As an application of this enamine activation we describe the organocatalytic step in the construction of (−)-bitungolide F (**18**) skeleton published recently by Cossy and coworkers (Scheme 44.1) [31]. This natural product is a polyketide isolated by Tanaka *et al.* [32] from the Indonesian sponge *Theonella cf. swinhoei*, which exhibits cytotoxic effects against 3Y1 rat normal fibroblast cells and inhibition toward VH1-related (VHR) dual-specificity phosphatase. The total synthesis of **18** starts with a previously reported enantioselective organocatalyzed Michael addition [33] providing enantioenriched aldehyde **17**, the key intermediate in the synthetic route. After eight more additional steps the target molecule **18** is obtained in 11% overall yield.



Scheme 44.1 Synthesis of (−)-bitungolide F (**18**) via an enantioselective organocatalyzed Michael addition.

A Michael addition procedure is also the organocatalytic step in the preparation of alkaloids dihydrocorynantheol [34–36] and protoemetinol [34, 36] developed by Ma and coworkers (Scheme 44.2). The authors envisioned that intermediate **19** could be further transformed into different active alkaloids by connecting it with a tryptamine, as the main core of the final products.



Scheme 44.2 Syntheses of tryptamine derived alkaloids via an enantioselective organocatalyzed Michael addition.

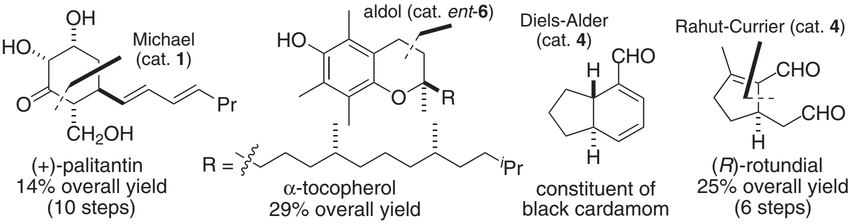


Figure 44.3 Natural products synthesized via dienamine catalysis.

44.2.2
Dienamine Catalysis

A less explored mode of activation within aminocatalysis is the so-called dienamine catalysis [37]. In this case it is an α,β-unsaturated carbonyl compound with a proton in the γ position suitable for deprotonation that after condensation with a chiral amine provides a reactive nucleophile, but now two activated positions are available, making possible both α- and γ-functionalization of the substrate. This vinylogous enamine can also act as an electron-rich diene. Work published in this area is very scarce to date, and only a few examples of its application in total synthesis have appeared in recent years: (+)-palitantin [38], α-tocopherol [39], a pungent constituent of black cardamom [40], and (*R*)-rotundial [41] (Figure 44.3).

44.2.3
Iminium Catalysis

Aminocatalysis has also been successfully applied for the activation of α,β-unsaturated carbonyl compounds to conveniently activate the β-position through a reactive iminium ion, a more electrophile specie than the corresponding conjugated system [42]. The electron-deficient iminium intermediate can be further trapped by incoming electron-rich nucleophiles, allowing the synthesis of final adducts with excellent levels of enantioselectivities. As well as enamine catalysis, iminium catalysis has been widely applied in natural product synthesis. Some representative applications of syntheses employing this LUMO-lowering iminium catalysis as one of the key steps, are (+)-ricciocarpin A [43], (+)-fawcettimine [44], (*S*)-warfarin [45], (*S*)-rolipram [46], dysideaproline [47], INCB018424 [48], iriomoteolide 1b [49], psymberin [50], (+)-minfiensine [51], and diazonamide A [52] (Figure 44.4).

MacMillan's group has worked intensively in the field of iminium catalysis, establishing a broad scope of applicability using this kind of activation and contributing actively to the development of this area. An elegant example is the three-step total synthesis of (+)-frondosin B in 50% overall yield [53], a member of a marine sesquiterpene family that exhibits significant properties in several therapeutic areas (Scheme 44.3) [54].

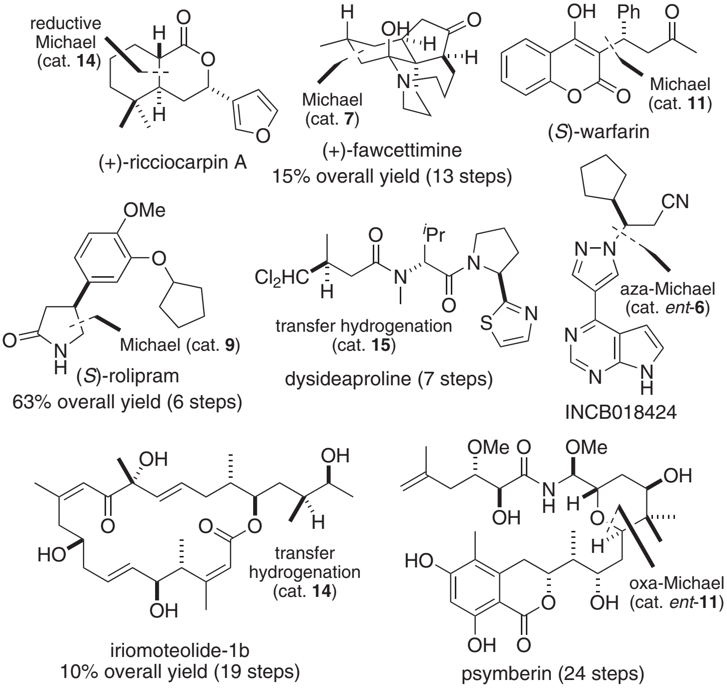
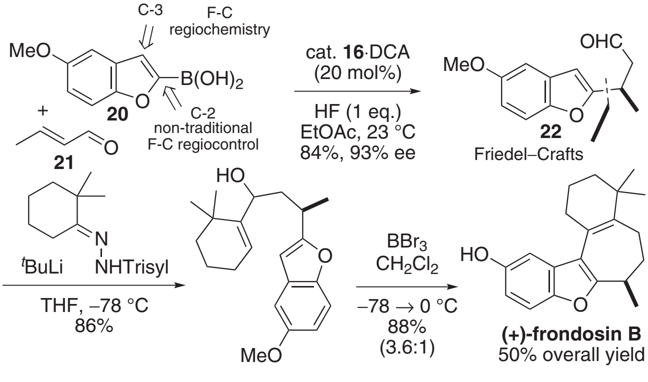


Figure 44.4 β-Functionalization of carbonyl compounds via iminium catalysis applied in total synthesis.

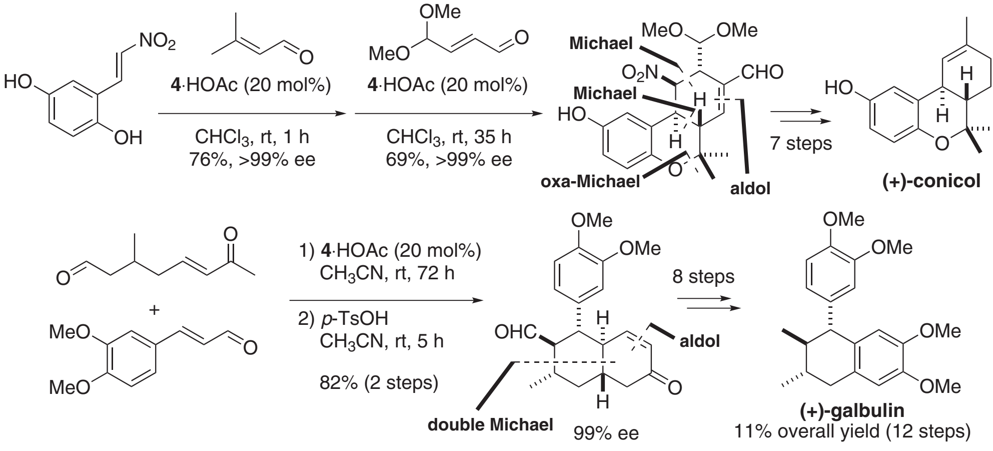


Scheme 44.3 Total synthesis of (+)-frondosin B via an iminium organocatalyzed Friedel–Crafts reaction.

The key step of this synthetic route is an iminium organocatalyzed Friedel–Crafts reaction of an *in situ* generated activated boronate **20** intermediate and crotonaldehyde (**21**), forming a non-traditional Friedel–Crafts adduct **22**, as the result of an unexplored regioselectivity (C2 versus C3). Additionally, the feasible structural variations on the starting heteroaryl trifluoroborate salt could allow straightforward access to various natural product analogues.

44.2.4
Organocascade Catalysis: Combinations of Enamine and Iminium Catalysis [55]

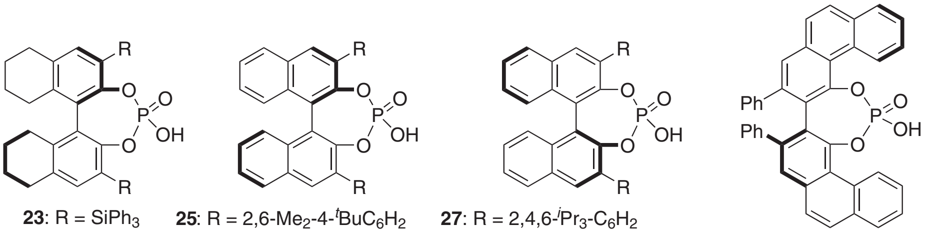
In recent years, multicomponent [56] and domino [57] reactions have attracted the attention of a wide number of research groups due to the growing interest in atom economy and sustainable chemistry by the scientific community. Attractive achievements have been accomplished recently in the field of organocatalysis, as applied in the synthesis of important targets. Some extraordinary examples have been presented by MacMillan and coworkers. One is the synthesis of (–)-aromadendranediol via a Mukaiyama–Michael–aldol condensation, through a triple-catalysis-cycle-specific mechanism involving cross-metathesis and iminium and enamine catalysis [58]. In addition, more recent examples are the total syntheses of six well-known alkaloids (strychnine, aspidospermidine, vincadifformine, akuammicine, kopsanone, and kopsinine) based on the combination of collective synthesis of natural products and organocascade catalysis [59]. Additional remarkable straightforward applications of organocascade catalysis have been published by Hong and coworkers. For instance, Scheme 44.4 depicts the first asymmetric total synthesis of (+)-conicol accomplished through an organocatalytic domino process oxa-Michael–Michael–Michael–aldol condensation, in a one-pot two-step reaction [60]. Another interesting example is the synthesis of (+)-galbulin via an organocatalytic domino Michael–Michael–aldol condensation, schematically represented in Scheme 44.4 [61].



Scheme 44.4 Total syntheses of (+)-conicol and (+)-galbulin via cascade organocatalytic reactions.

44.3
Hydrogen Bond Catalysis in Total Synthesis

Catalysts acting by hydrogen bond interactions have contributed significantly to progress in this area [62]. Among the numerous chiral acid catalysts recently



23: R = $SiPh_3$
24: R = Ph
25: R = 2,6-Me_2-4-^{t}BuC_6H_2
26: R = 9-phenanthryl
27: R = 2,4,6-^{i}Pr_3-C_6H_2
28: R = 2,6-^{i}Pr_2-4-(adamant-1-yl)-C_6H_2
29: R = β-naphthyl
30

Figure 44.5 Chiral phosphoric acid derivatives utilized as organocatalysts.

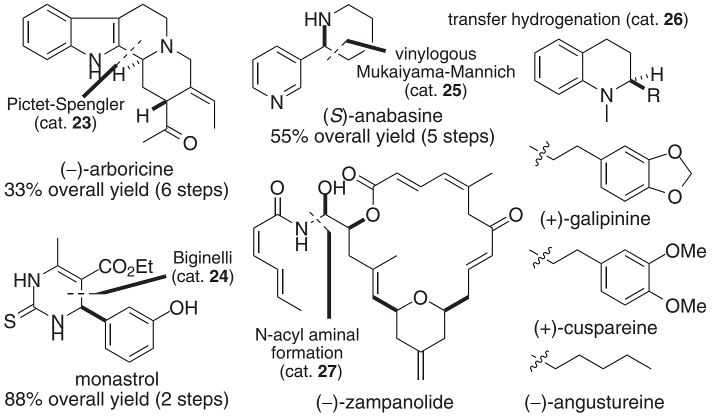


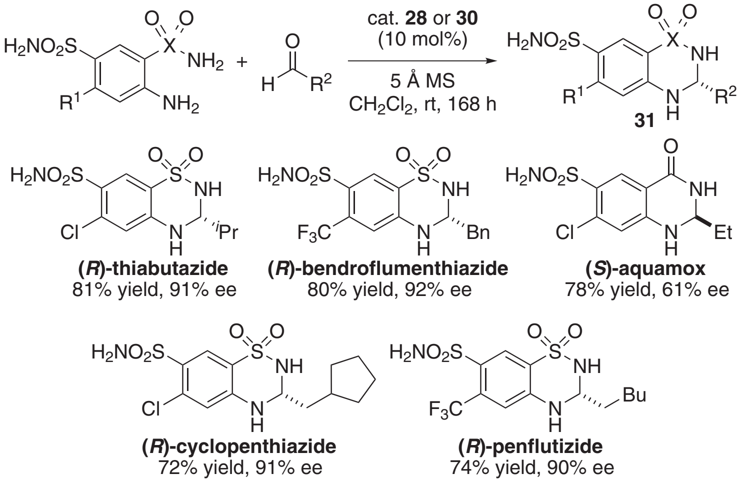
Figure 44.6 Remarkable Brønsted acid catalyzed natural product syntheses.

developed and successfully applied as organocatalysts, chiral phosphoric acids and chiral (thio)urea have become two pivotal research areas in organocatalysis.

44.3.1
Phosphoric Acids

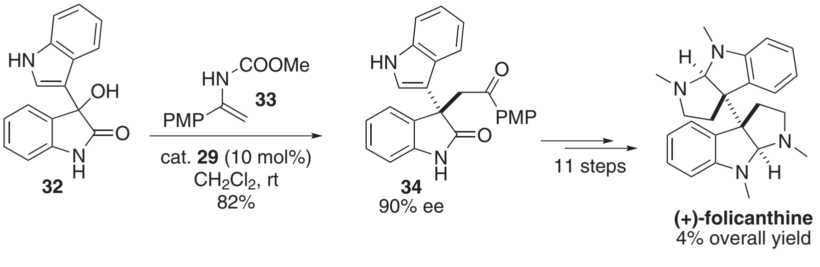
Since pioneering works reported in 2004 by Terada [63] and Akiyama [64], chiral phosphoric acids have rapidly emerged as a new potent class of Brønsted acid catalysts with remarkable synthetic power owing to their continuous application in the development of new organocatalytic methodologies and resulting in a significant expansion of this field (Figure 44.5) [65]. Proof of this substantial progress is the employment of such a privileged class of Brønsted acids in the total syntheses of significant compounds such as (−)-arboricine A [66], (*S*)-anabasine [67], monastrol [68], (−)-zampanolide [69], (+)-galipinine [70, 71], (+)-cuspareine [70], (−)-angustureine [70, 72], and torcetrapib (Figure 44.6) [73].

List and coworkers have published a practical and useful approach to chiral aminals **31** starting from aldehydes and employing chiral phosphoric acids as suitable catalysts. The authors applied this novel procedure in the straightforward synthesis of several benzo(thia)diazines pharmaceuticals, including (*S*)-aquamox, (*R*)-thiabutazide, (*R*)-penflutizide, (*R*)-bendroflumethiazide, and (*R*)-cyclopenthiazide with excellent enantioselectivities in one reaction step (Scheme 44.5) [74].



Scheme 44.5 Brønsted acid catalyzed synthesis of pharmaceutically relevant compounds.

More recently, a Brønsted acid organocatalyzed nucleophilic substitution reaction of 3-hydroxindoles **32** with ene-carbamates **33** was successfully developed by Gong's group for its application in the first catalytic enantioselective synthesis of (+)-folicanthine [75], a member of the large cyclotryptamine alkaloid family that exhibit fascinating biological and pharmaceutical activities [76]. The 3,3′-disustituted oxindole intermediate **34** with a chiral quaternary stereogenic center is the key chiral building block in this synthetic route (Scheme 44.6).



Scheme 44.6 Total synthesis of (+)-folicanthine.

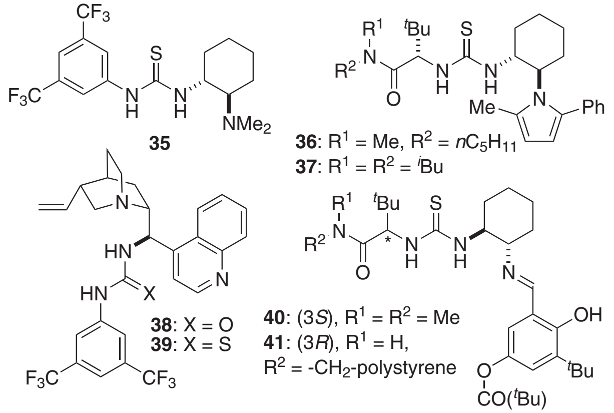


Figure 44.7 (Thio)ureas as organocatalysts in natural product synthesis.

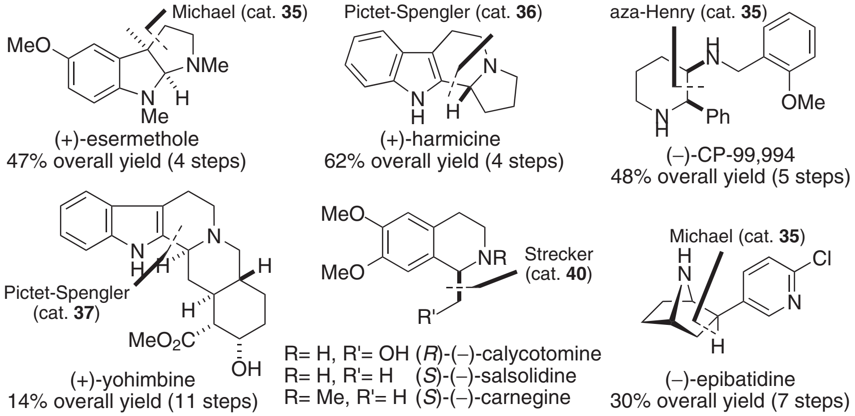
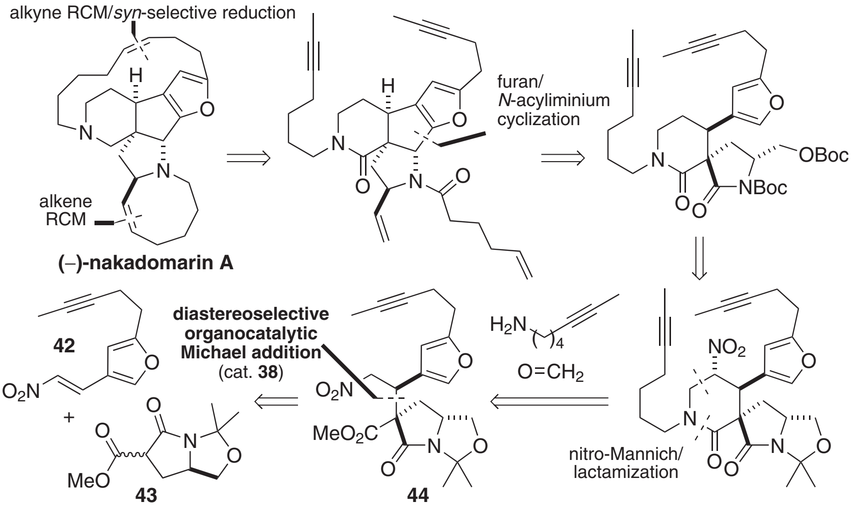

Michael (cat. 35)
(+)-esermethole
47% overall yield (4 steps)
Pictet-Spengler (cat. 36)
(+)-harmicine
62% overall yield (4 steps)
aza-Henry (cat. 35)
(−)-CP-99,994
48% overall yield (5 steps)
Pictet-Spengler
(cat. 37)
(+)-yohimbine
14% overall yield (11 steps)
Strecker
(cat. 40)
R= H, R'= OH (R)-(−)-calycotomine
R= H, R'= H (S)-(−)-salsolidine
R= Me, R'= H (S)-(−)-carnegine
Michael (cat. 35)
(−)-epibatidine
30% overall yield (7 steps)

Figure 44.8 Significant total syntheses involving (thio)urea catalysts.

44.3.2
(Thio)urea Organocatalyzed Processes

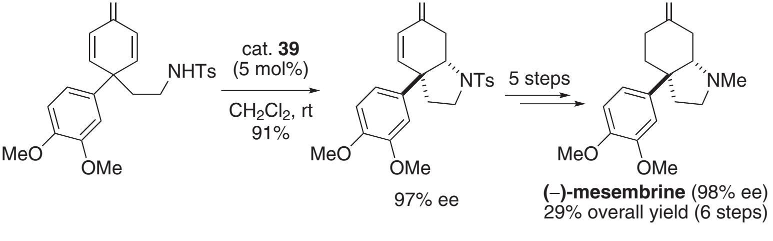
A different class of catalysts acting by hydrogen bond interactions covers the large group of (thio)urea derivatives (Figure 44.7). Although the application of this family of catalysts seems to be limited in comparison with Lewis acids due to their weaker hydrogen bonding, the concept of bifunctionality, by analogy with the catalytic action of some enzymes, has been investigated extensively in this area in order to increase their efficiency. In this context, intensive efforts have been devoted to studying the behavior of such structures as appropriate catalysts in a wide number of valuable organocatalytic processes [77]. Many of these chiral (thio)ureas have already been involved in the synthesis of remarkable molecules, such as (+)-esermethole [78], (+)-harmicine [79], (−)-CP-99,994 [80], (+)-yohimbine [81], (*R*)-(−)-calycotomine [82], (*S*)-(−)-salsolidine [82], (*S*)-(−)-carnegine [82], and (−)-epibatidine [83] (Figure 44.8).

An elegant 19-steps synthesis of (−)-nakadomarin A has been reported by Dixon and coworkers (Scheme 44.7) [84]. It is a marine hexacyclic alkaloid that exhibits impressive biological activities [85], and a challenging complex structure for its total synthesis. A key step in this synthetic route is the diastereoselective organocatalyzed Michael addition between β-keto ester **43** and nitroalkene **42**. For a high diastereoselectivity (dr 18 : 1 : 0 : 0) and short reaction time, bifunctional urea **38** was required, affording intermediate **44** as a single diastereomer in 81% yield after isolation.


alkyne RCM/*syn*-selective reduction
alkene RCM
(−)-nakadomarin A
furan/ *N*-acyliminium cyclization
OBoc
NBoc
42
43
44
diastereoselective organocatalytic Michael addition (cat. 38)
H_2N
$O=CH_2$
O_2N
MeO_2C
MeO
NO_2
nitro-Mannich/ lactamization

Scheme 44.7 Retrosynthetic analysis of (−)-nakadomarin A.

Another example of the use of thiourea catalysts in total synthesis was reported by You and coworkers, who obtained (−)-mesembrine by means of an organocatalyzed aza-Michael addition process (Scheme 44.8) [86]. The crucial step in this route is based on a previous study of the desymmetrization of cyclohexadienones performed by the same research group [87]. On this occasion, the difficult task of controlling the sterically congested chiral arylated quaternary carbon center was



Scheme 44.8 Enantioselective synthesis of (−)-mesembrine via desymmetrization of cyclohexadienones.

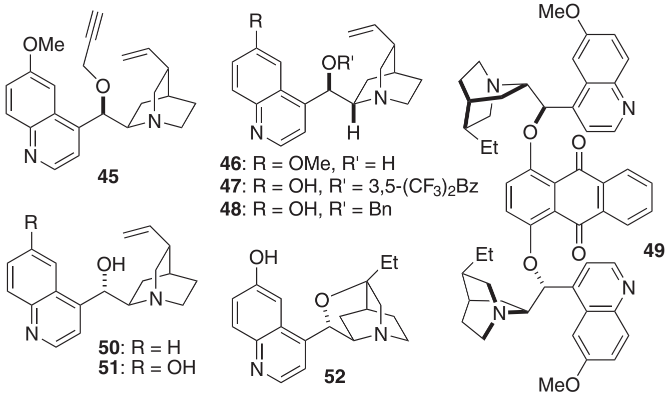


Figure 44.9 Efficient cinchona alkaloids as organocatalysts.

reached by the use of bifunctional thiourea **39**, which facilitated the desymmetrization process [88] with high yield and enantioselectivity (91%, 97% ee).

44.4
Cinchona Alkaloids in Total Synthesis

Cinchona alkaloids, natural products extracted from *Cinchona officinalis*, have been extensively utilized in medicine as well as for chiral ligands in metal catalysis [89]. Moreover, in the last decade these compounds have been shown to be powerful organocatalysts (Figure 44.9), used as Lewis or Brønsted base, and also acting as bifunctional catalysts in numerous examples [90]. Significant outcomes have been reached in this field, such as the total synthesis of pregabalin [91], (*S*)-baclofen [92], (+)-biotin [93], SNAP-7941 [94], (−)-mycestericin E [95], (+)-calanolide A [96], (+)-inophyllum B [96], DPP-4 inhibitor [97], manzacidins A and C [98], (+)-fostriecin, and (+)-phoslactomycin B [99] (Figure 44.10).

In the following examples, using cinchona alkaloid catalysis, the key step of the syntheses is an asymmetric organocatalytic Henry reaction between a ketone and nitromethane. For example, Wang's group published the total synthesis of (*R*)-(+)-dioxibrassinin as an application of their method for the synthesis of chiral 3-hydroxy-2-oxindoles, which are important motifs in various natural products and drugs (Scheme 44.9) [100]. In a second example, Gomez Pardo, Cossy, and coworkers reported the synthesis of SSR 2415686 [101], an active drug in the treatment of schizophrenia and irritable bowel syndrome (Scheme 44.9). The construction of stereogenic quaternary centers is still an active and challenging task in organic chemistry [102]. In both strategies, ketones, as less explored substrates in organocatalytic Henry reaction [103], were used, allowing achievement of the required chiral centers with excellent enantioselectivities.

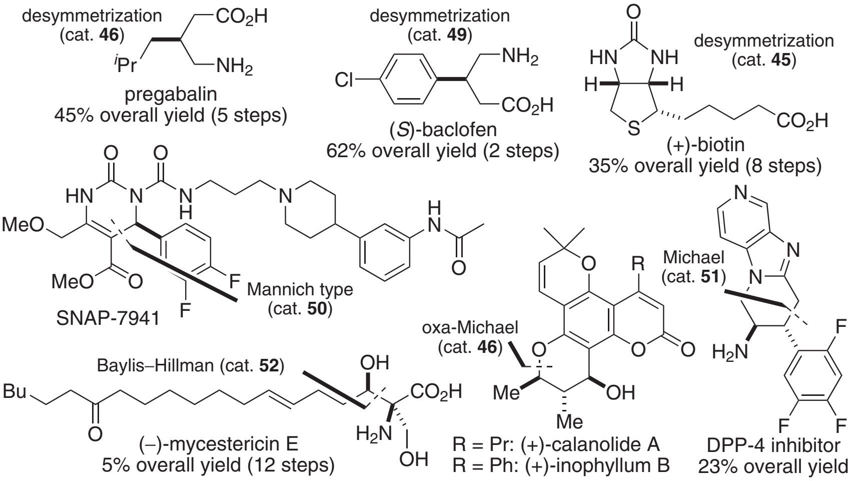
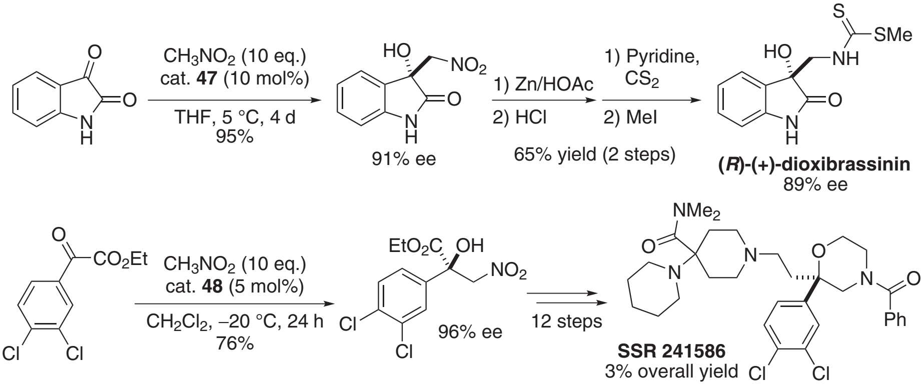


Figure 44.10 Target molecules synthesized using cinchona alkaloid organocatalysts.



Scheme 44.9 Total syntheses of (*R*)-(+)-dioxibrassinin and SSR 241586 via organocatalyzed Henry reactions.

44.5
Phase-Transfer Catalysis in Target Molecule Synthesis

Although the term phase-transfer catalysis was introduced in 1971 by Starks [104], this field has received particular attention in recent decades. The use of chiral ammonium salts as catalysts (Figure 44.11) has been recognized as an effective tool for organic synthesis and much time has been spent in both industrial and academic sectors, making possible the development of numerous highly enantioselective processes [105]. The applicability of phase-transfer catalysis (PTC) has

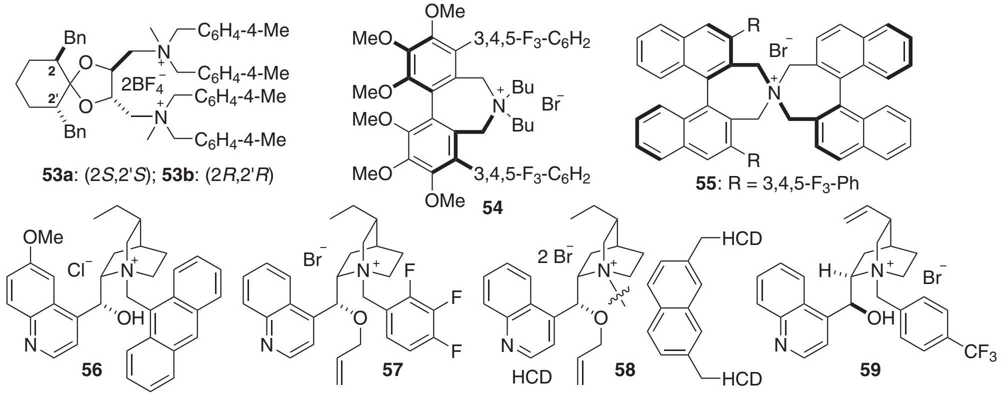


Figure 44.11 Model phase-transfer catalyst structures.

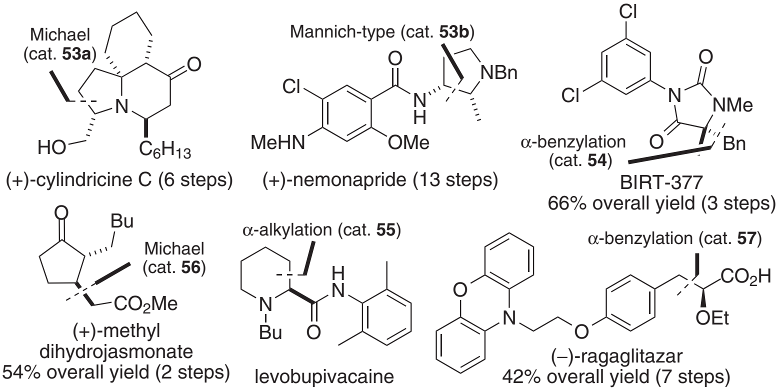
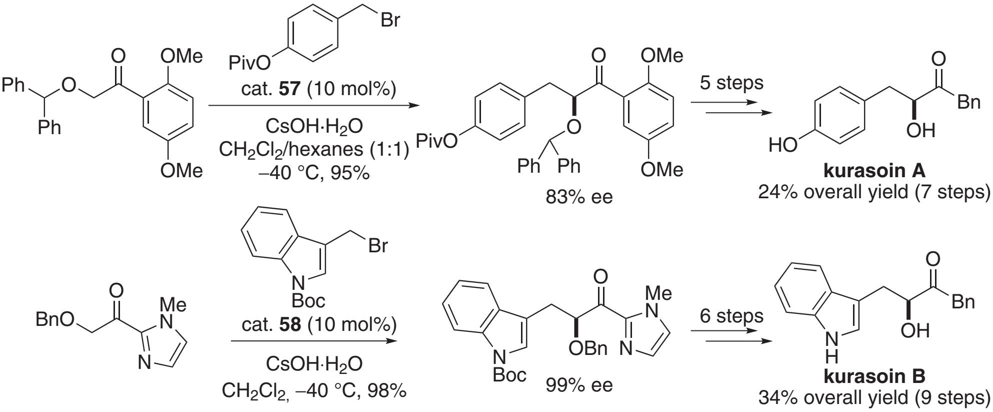


Figure 44.12 Appealing compounds synthesized by phase-transfer catalysis.

been well demonstrated by the asymmetric synthesis of valuable active targets, such as (+)-cylindricine C [106], (+)-nemonapride [106, 107], BIRT-377 [108], (+)- and (−)-methyl dihydrojasmonate [109], levobupivacaine [110], and ragaglitazar [111] (Figure 44.12).

The highly enantioselective syntheses of kurasoin A and B reported by Andrus and coworkers are illustrative examples of the utility of phase-transfer catalysis. These compounds are protein farnesyltransferase (PFTase) inhibitors and were isolated for the first time from the fermentation broth of the soil fungus, *Paecilomyces* sp [112]; owing to their potential anticancer properties [113], a few groups have invested efforts in the development of new asymmetric total syntheses [114]. Andrus's research group firstly synthesized kurasoin A in seven steps (24% overall yield) through a phase-transfer catalyzed benzylation reaction to afford the central core of this PFTase inhibitor [115]. Later, the same authors also applied a similar alkylation methodology to synthesize kurasoin B in a nine-step strategy (34% overall yield) (Scheme 44.10) [116].



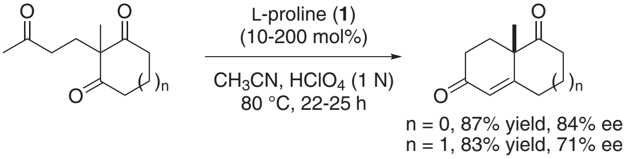
Scheme 44.10 Synthesis of kurasoin A and B by means of phase-transfer catalysis.

44.6
Industrial Applications of Organocatalysis

In the last four decades, the application of asymmetric catalysis in industry has increased, owing to the importance of synthesizing chiral drugs in the pharmaceutical sector [117]. Despite its short history, a few organocatalytic methodologies have also been successfully extrapolated to industrial applications. Nowadays, intensive efforts are increasingly invested in this direction, in order to scale-up organocatalytic procedures [118]. In such procedures, handling high amounts of catalyst could be easier and less toxic, since organocatalysts present some advantages compared to transition metal catalysts, such as their stability or recovery, and consequently are becoming an attractive alternative and a suitable solution in the industrial sector. In this section, we briefly introduce some relevant industrial organocatalytic processes.

44.6.1
Aminocatalysis in the Industrial Sector

Most probably, the first and more significant industrial example of an asymmetric organocatalyzed process is the well-known Hajos–Parrish–Eder–Sauer–Wiechert reaction [119], independently discovered by two research groups in 1971 (Scheme 44.11) [120]. These two groups, belonging to Schering and Hoffmann-La Roche industrial companies, have implemented this reaction since the early 1970s to manufacture steroids on multi-kilogram scales.



Scheme 44.11 L-Proline (**1**) catalyzed Hajos–Parrish–Eder–Sauer–Wiechert annulation reaction.

This intramolecular aldol reaction has attracted attention from the beginning, for example, due to the easy access to steroid precursors octahydronaphthalenedione **60** and tetrahydroindanone **61**, starting from readily available raw materials, and using commercially available L-proline catalyst (Figure 44.13) [121].

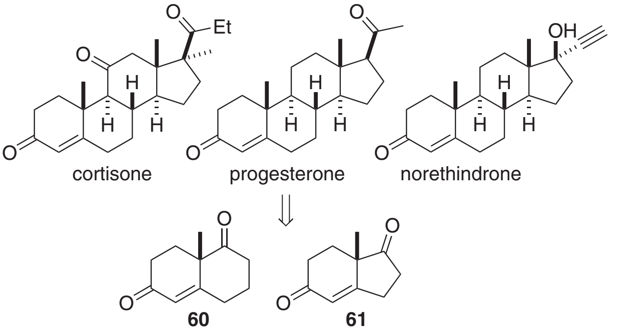
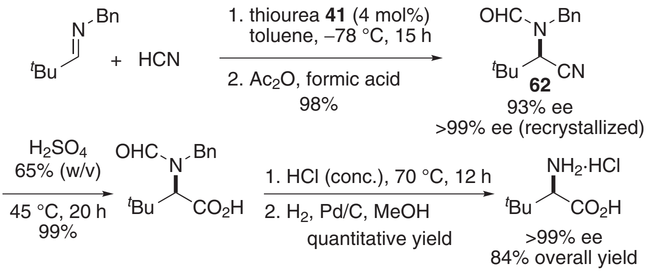


Figure 44.13 Relevant industrial commercialized steroids.

44.6.2
Thiourea Catalysis at the Industrial Scale

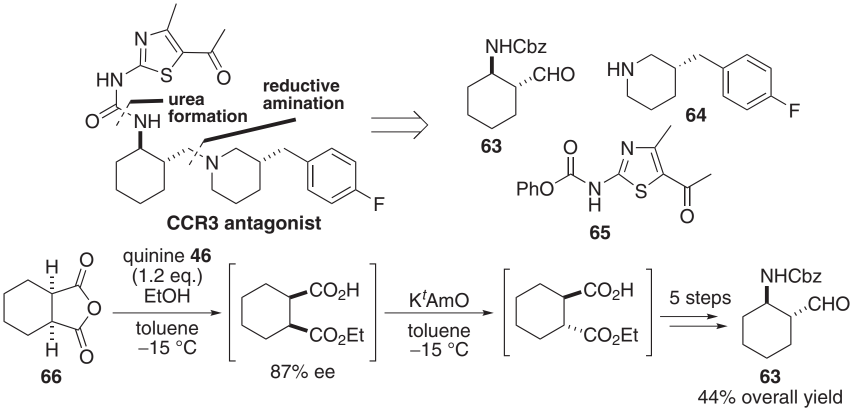
Another significant example utilized commercially is an asymmetric organocatalytic Strecker reaction [122], the most classical approach for the enantioselective preparation of α-amino acids. In this context, the methodology developed by Jacobsen and coworkers has been employed by Rhodia ChiRex for the large-scale synthesis of chiral amino nitriles **62** as useful building blocks for further transformation into natural and unnatural amino acids (Scheme 44.12) [123]. The high efficiency of this process is demonstrated by the small amount of catalyst **41** (4 mol%) necessary to provide final aminonitriles **62** in high yield and enantioselectivity.



Scheme 44.12 Organocatalyzed synthesis of α-amino acids.

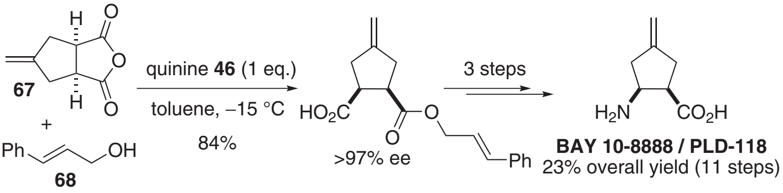
44.6.3
Cinchona Alkaloids at the Industrial Level

As shown in Section 44.4, cinchona alkaloids have been used in several desymmetrization processes. In this field, Yue and coworkers have disclosed the stereoselective synthesis of a CCR3 antagonist, with potential activity in the prevention of inflammation in asthma and allergic rhinitis, in a 20-kg pilot-plant manufacture [124]. The authors designed the synthesis from fragments **63–65**, through a reductive amination between fragment **63** and **64**, and urea formation with fragment **65**. The synthetic route for preparation of the key fragment **63** starts from quinine-mediated opening of *meso*-hexahydrophthalic anhydride (**66**) with EtOH and involves seven steps with an overall yield of 44% (Scheme 44.13).



Scheme 44.13 Retrosynthetic analysis of CCR3 antagonist, and synthesis of **63** through a desymmetrization reaction.

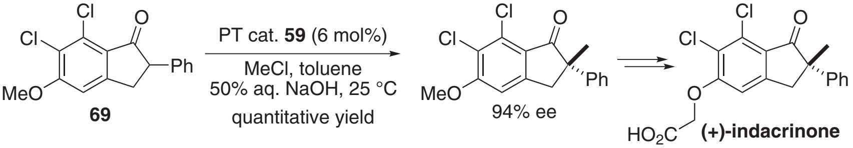
A desymmetrization step was also envisioned by a research group at Bayer AG to synthesize a new antifungal agent, BAY 10-888, in multi-kilogram quantities in a pilot plant [125]. After screening different alcohols for the desymmetrization of the anhydride **67**, *trans*-cinnamyl alcohol (**68**) in the presence of stoichiometric amounts of quinine **46** provided the best results, suitable for carrying out the process on a pilot-plant scale (Scheme 44.14).



Scheme 44.14 Synthesis of BAY 10-888 through an organocatalytic desymmetrization reaction.

44.6.4
Phase-Transfer Catalysis in Industry

Phase-transfer catalysts are perhaps one of the most employed organocatalysts at the industrial scale. The first phase-transfer catalyzed reaction carried out in industry was developed by Merck Company in the mid-1980s [126]. This pioneering methodology was applied to the methylation reaction of cyclic ketone **69** in the presence of chiral ammonium salt **59** to create a chiral quaternary center. The process was developed with the objective of synthesizing (+)-indacrinone (MERCK-0197), a chiral indanone with diuretic properties and commercialized as a uricosuric drug. The potential of this procedure is also reflected in economic aspects of the production, since the resultant catalytic process is less expensive than the obtainment of the active isomer by resolution from the corresponding racemate [126c] (Scheme 44.15).



Scheme 44.15 Enantioselective synthesis of (+)-indacrinone.

44.7
Conclusions

This chapter has presented motivating applications of organocatalysis in the synthesis of relevant biological active compounds. The most common organocatalytic approaches, such as aminocatalysis, hydrogen bond catalysis, cinchona alkaloids catalysts, and phase-transfer catalysis have been covered. We hope the reader now has a general overview of the great utility of organocatalysis in total synthesis as well as at an industrial level. The examples highlighted here show that this kind of catalysis has become a powerful tool in the field of asymmetric oriented synthesis, being complementary to transition metal catalysis as well as enzymes. However, despite all these examples, organocatalysis is still in its infancy and there is still a long way to go. Although the role of organocatalysts is still unclear in some cases, many efforts are focused on understanding the mechanism of the processes, which will allow us to overcome several drawbacks like the need for high catalyst loadings and long reaction times. As a result, in the near future, this will assist in the development of new more complex examples of remarkable syntheses and the expected scaling-up to commercial applications.

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Appendix

A section of chiral organocatalysts is presented here. Compounds are classed according to the chiral inductor classes present in their structure. References below the molecules refer to the corresponding chapter Figure/Chart, Scheme or Table where further information on typical reaction scope can be found.

Contents

Proline Derivatives and Proline Analogs
  a) Substituted Prolines
  b) Proline Tetrazole Catalysts and Analogs
  c) Prolinamides
  d) Prolinamines
  e) Diarylprolinol Derivatives
  f) Chiral Pyrrolidines
  g) Phosphorus Derivatives
  h) Thioethers and Acetals
  i) Onium Salts
  j) *N*-Oxides
  k) Piperazine Derivatives
  l) Ionic Liquid Tagged Proline Derivatives
  m) Polymer-Supported Prolines/Pyrrolidines
  n) Polymer-Supported Prolinamides
  o) Polymer-Supported Diarylprolinols
  p) Silica-Supported Derivatives
  q) Proline Analogs

Non-Proline Amino Acids
  a) Unmodified α-Amino Acids
  b) Protected Amino Acids
  c) *N*-Aryl Valinamide Derivatives
  d) (Thio)ureas

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  e) Supported Amino Acids
  f) Miscellaneous

Chiral Imidazolidinones (MacMillan's Catalysts and Analogs)
  a) "First-Generation" Imidazolidinone Catalysts
  b) Supported "First-Generation" Imidazolidinone Catalysts
  c) "Second-Generation" Imidazolidinone Catalysts

Di- and Oligopeptide Catalysts
  a) Proline-Containing Di- and Oligopeptides
  b) Cyclic Dipeptides
  c) Non-Proline Oligopeptides

Cinchonas
  a) Cinchonidine, Quinine, Cupreine, Quinidine, Cinchonine and Cupreidine Derivatives
     Supported Catalysts
     Bis-Cinchonas
     Onium Salts
  b) 9-Aza-Cinchona Derivatives
     The CN-QD Series
     The CD-QN Series
     (Thio)ureas
     Miscellaneous

Planar Chiral Catalysts
  a) Metallocenes
  b) Helicenes
  c) Others

Biaryl Catalysts
  a) Binaphthyl Catalysts
  b) Bis-Tetralins
  c) Biphenyl/Bipyridyl Catalysts
  d) Spirobiindanes
  e) Miscellaneous

1,2-Diamines
  a) α-Amino Acid-Derived Diamines
     Primary/Secondary Diamines
     Primary/Tertiary Diamines
     Amino Amides
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  b) 1,2-Diaminocyclohexane Derivatives
  c) Diphenylethylenediamine Derived Catalysts
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1,2-Aminoalcohols
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  b) Others

1,2-Aminophosphines

TADDOL-Derived Catalysts

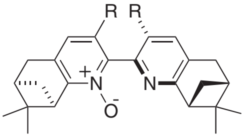
Carbohydrate-Derived Catalysts

Terpene-Derived Catalysts

Chiral Sulfoxides

Miscellaneous
  a) Cyclic Guanidines
  b) Tetramisol Analogs
  c) Imidazolines
  d) Chiral Phosphines
  e) Molecular Tweezers
  f) Unclassed Catalysts

Key:
F = Figure or Chart; S = Scheme; T = Table.
Example:

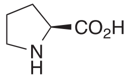


R = H 15.F2; 8
R = Me 15.F2; S4

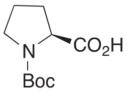
Catalyst with R = H is discussed in Chapter 15 (see in Figures 15.2 and 15.8); Catalyst with R = Me is discussed in Chapter 15 (see in Figure 15.2 and Scheme 15.8).

Proline Derivatives and Proline Analogs

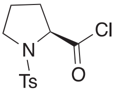
a) Substituted Prolines



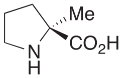
1.F1
9.F4
21.S8; S5; 6; 7; 15; 16; 17; 18; 19; 21; 29; 30; 32; 33; 34; 35
22.S1; 2; 3; 4; 5; 11; 13
24.F7
26.S2
27.S7; 18
28.T1; 4; 5; 6; S2; 32; 34; F2
31.F4.3; 4.4; S2.9; 4.31; 4.32; 4.33
33.F5; S1; S2
36.S1; 2; 21
38.S43
42.S1; 2; 3; 6; 9
44.F1; S11



43.S20



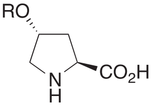
41.F11



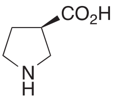
25.S1
36.S5

$[HPro]_2SO_4$
22.S18

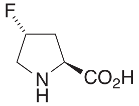
[emim][Pro]
22.S14; 15; 16; 17



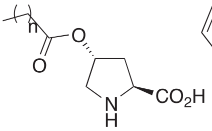
R=H 23.F4
R=TBDPS 21.S20
24.F9
28.T3
R=TBS 24.F36
27.S8
R=^{t}Bu 27.F2



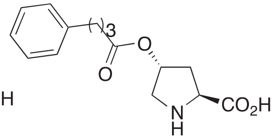
28.T5; S6



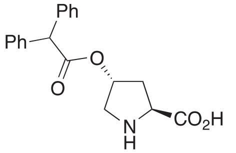
28.S4; 6; 7; 8
36.S4



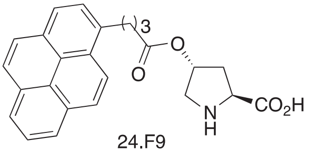
24.F9



24.F9



24.F9



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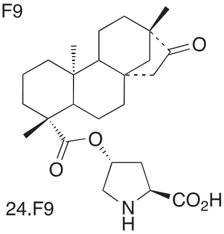

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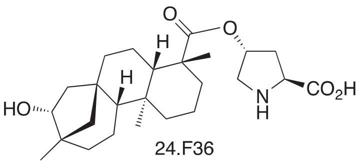
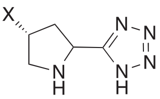
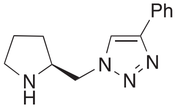


24.F36

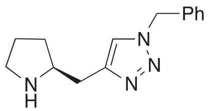
b) Proline Tetrazole Catalysts and Analogs



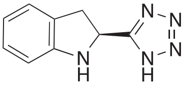
S, X = H 1.S8; F1; 2
22.S9
24.S4
33.F5
34.S1
44.F1; S9
S, X = OTBDPS 24.F36
R, X = H 27.F2



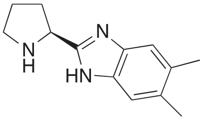
1.F6
24.F23



1.F6

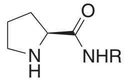


37.S13

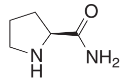


27.S8

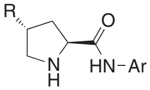
c) Prolinamides



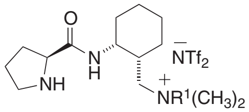
1.F1; 2



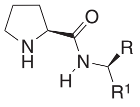
1.F3
31.F4.4
44.F1; S13; 14



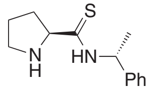
R = H, Ar = Ph 1.F3
R = H, Ar = 3-nitrophenyl 1.F3
24.F18 (HBr)
R = H, Ar = perfluorophenyl 1.F3
R = H, Ar = 6-methylpyridin-2-yl 1.F3
R = H, Ar = 3-chloro-5-fluoro-2-hydroxyphenyl 24.F18 (TFA)
R = OBn, Ar = pyridin-4-yl 1.F3



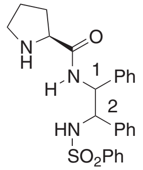
R^1 = Et or *n*-Bu 22.S27



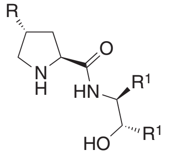
R = Ph, $R^1 = CH_3$ 25.F13
R = Bn, R^1 = COOH 24.F30



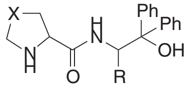
1.F3
25.F13
28.T3 (Cl_2CHCO_2H)



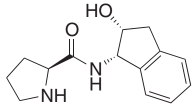
1R, 2R 25.F13
1R, 2S 25.F13



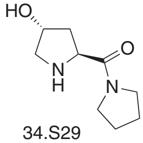
R = H, $R^1 = CO_2Et$ 24.F19
R = OTBS, $R^1 = CO_2Et$ 24.F19
R = H or OTBS, $R^1 = CO_2Et$ 1.F3
R = OTBDPS, $R^1 = CO_2Et$ 28.T3
R = H, R^1 = Ph 22.S8



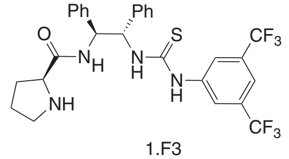
S,*S*, X = C, R = Ph 25.F13 28.T3
S,*S*, X = C, R = i-Bu 1.F3 25.F13 28.S5
S,*S*, X = S, R = i-Bu 25.F13
R,*R*, X = C, R = i-Bu 28.S5



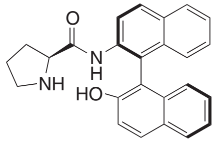
1.S3



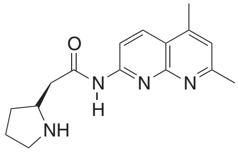
34.S29



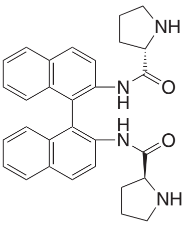
1.F3



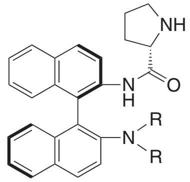
24.F16



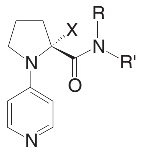
9.F3



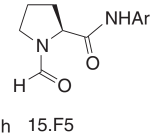
(*R*$_a$)-binam-*L*-Pro 1.F3
(*S*$_a$)-binam-*L*-Pro 24.F16



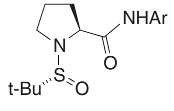
R = $C_{12}H_{25}$ 1.F3



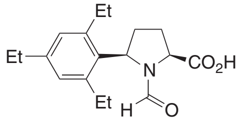
X = Me 41.F1
X = H, R = Ph, R' = Bn 41.F1



Ar = Ph 15.F5
32.F3; T1; T2
Ar = 1-Naphthyl 15.F5
32.F3; T1; T2

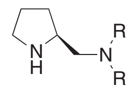


Ar = 3,5-$Me_2C_6H_3$ 15.F5
32.F3; T1
Ar = 2,6-i-$Pr_2C_6H_3$ 15.F5
24.S7
Ar = 3,5-i-$Pr_2C_6H_3$ 32.F3; T1; S23

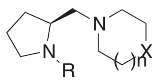


(2S,5R) 15.F5
32.F3; T1; T2

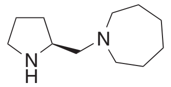
d) Prolinamines



$R=C_2H_5$ 24.F25
$R=C_{10}H_{21}$ 1.F5
24.F18; 25 (TFA)
28.F5; T3 (TFA)
34.S1

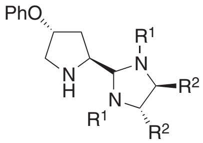


R = H, X = C, n = 0 1.F5
31.F4.3
42.S4
34.S1
38.S11
40.S36

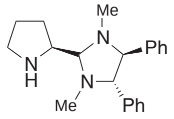


$H_4SiW_{12}O_{40}$

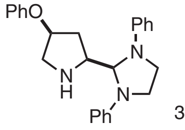
24.F25



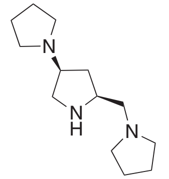
27.F2



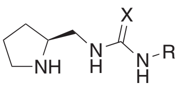
34.S30



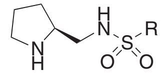
33.S10; F5
34.S33
42.S13



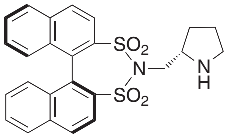
1.F5



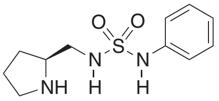
X = S, R = Ar 1.F1; 2
X = O, R = $(CF_3)_2C_6H_3$ 12.F6
X = S, R = $(CF_3)_2C_6H_3$ 12.F6
X = S, R = 3,5-$(CF_3)_2$-Ph 1.F8
34.S1
X = S, R = 4-Me-C_6H_4 12.F6
24.F26
X = S, R = *tert*-butyl 12.F6
X = S, R = cyclohexyl 12.F6
X = S, R = 1-naphtyl 12.F6
X = S, R= 4-C_8F_{17}-Ph 27.S22
X = N, R = 2,6-diisopropylphenyl 1.F8



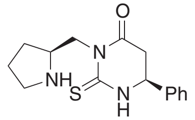
R 1.F1; 2
R = C_4F_9 28.S33; T3
24.F18; 26
R = CF_3 1.F7
12.F6
34.S1
R = 3,5-$(CF_3)_2$-Ph 1.F7



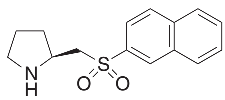
1.F7
24.F27



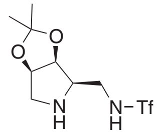
1.F8



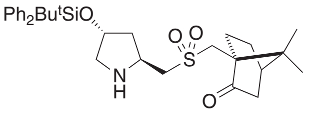
1.F8



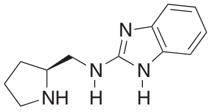
24.F27



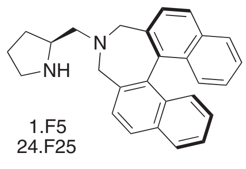
1.F7



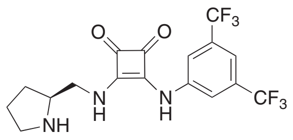
27.F2



1.F8
24.F26

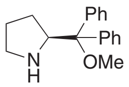


1.F5
24.F25

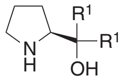


10.S37

e) Diarylprolinol Derivatives



44.F1; S1; 5

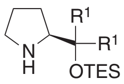


Ar 1.F1

Ar = Ph 21.S8
22.S9
31.F4.3; 4.4
33.S12
37.S2

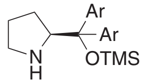
Ar = 3,5-$(CF_3)_2$-Ph 28.T2

Ar = 3,5-$(CH_3)_2$-Ph 27.S20



Ar = Ph 2.S1
38.S14
43.S29; 31
27.S8
37.F4

Ar = 3,5-$(CF_3)_2$-Ph 2.S1
36.S10
38.S3
44.F1; 5; 9



Ar = Ph

21.S23
25.S2; 3; 4; 5
27.S8; 17
33.F4; S7; 11; 13; 14; 17; 22
35.S1; 22; 23
38.S12; 15; 16; 31; 44; 45; 46; 47
43.S8; 10; 26; 30

2.F2; S1-12
24.F28; 34; 40
26.S6
31.F4.3; 4.4
34.S1; 34.S6; 21; 23; 26; 31; 34; 35
37.S1; 4; 5; 6; 14; 15
42.F3; S7; 8; 12; 13; 16; 17; 18; 19; 20; 21; 22
44.F1; S2; 4; 7; 9

Ar = 3,5-$(CF_3)_2$-Ph

24.F34; 36; 38; S8
27.S8
31.S4.34; F4.4
35.S1; 6; 24
36.S9
38.S3
43.S9; 11; 12; 27; 28

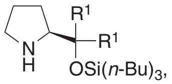
2.F2; S1-12
26.S6; 8
28.S7; T6
33.F4; S6; 8; 15; 18; 19; 20; 21; 23
37.F2
42.S10; 12
44.F1; S6; 12; 15

Ar = 4-OMe-3,5-^{t}Bu$_2$C$_6$H$_2$ 38.S14

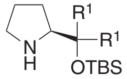
Ar = C_6H_4-4-CH_2NMe_2 22.S30; 31
24.F28
35.S1

Ar = 3,5-$(CH_3)_2$-Ph 37.S15

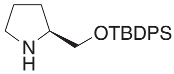
Ar = Naph 34.S6



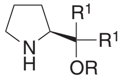
Ar = Ph 27.S19



Ar = Ph 1.F9
2.S1
33.S13



1.F9

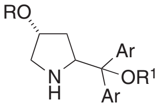


R = $SiPh_3$, $R^1 = C_6H_{11}$ 24.F34
25.S6
44.F1

R = TMS, $R^1 = C_6H_{11}$ 24.F34

R = H, $R^1 = C_6H_{11}$ 24.F34

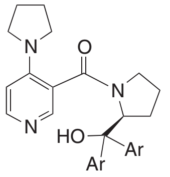
R = TMS, $R^1 = C_{12}H_{25}$ 34.S27



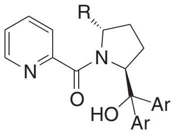
S, R = H, Ar = 3,5-$(CF_3)_2$Ph, R^1 = H 44.F1; S8; 9

S, R = TBS, Ar = Ph, R^1 = TMS 33.S6

R, R = Bn, Ar = Ph, R^1 = H 38.S4



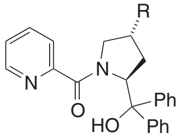
Ar = Ph 41.F1; 17



R = H; Ar = Ph 32.F3; T1

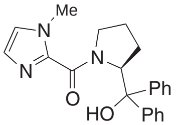
R = H; Ar = 3, 5-$Me_2C_6H_3$ 32.F3; T1

R = OPiv; Ar = Ph 32.F3; T1; S24



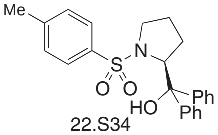
(S*)*, R = H 15.F6; S28

(2*S*,4*R*), R = OPiv 15.F6;



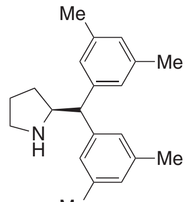
15.F6

32.F3; T1; S19

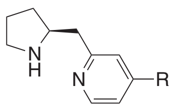


22.S34

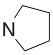
f) Chiral Pyrrolidines

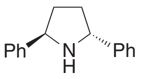


1.F9
38.S30

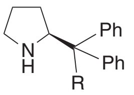


R = NMe_2 (DPYMP) 1.F9

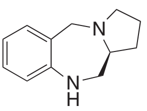
R =  (PPYMP) 1.F9
34.S1



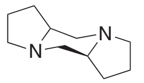
1.F10
27.S22



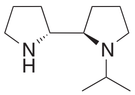
R = Ph 1.F10
27.S19
R = F 1.F10
R = N_3 1.F10



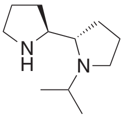
31.S4.12



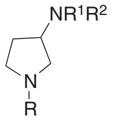
31.S4.12



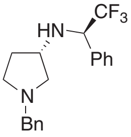
1.F5
34.S20; 28



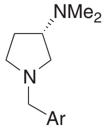
34.S1



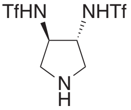
R, R = Bn, $R^1 = R^2 = H$	31.S4.12
R, R = CO_2Et, $R^1 = R^2 = CH_3$	31.S4.12
R, R = Bn, $R^1 = R^2 = CH_3$	31.S4.12
R, R = CH_3, $R^1 = R^2 = CH_3$	31.S4.12
R, R = NMe_2, $R^1 = R^2 = CH_3$	31.S4.12
R, R = Me, $R^1 + R^2$ = pyrrolidine	31.S4.12
S, R = Me, $R^1 = CH_3$, R^2 = Bn	31.S4.12
S, R = Me, $R^1 = CH_3$, $R^2 = CH_2Ar$	31.S4.12



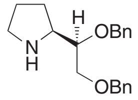
31.S4.12



Ar = 2-HOPh 31.S4.12
Ar = 3-HOPh 31.S4.12

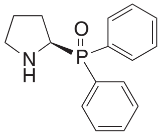


1.S19

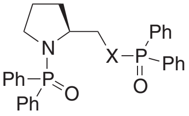


1.F9

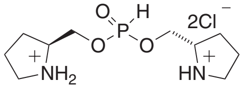
g) Phosphorus Derivatives



1.F9

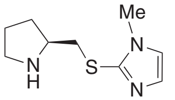


X = O 15.F5
X = NH 15.F5

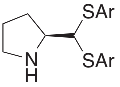


22.S9

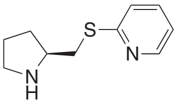
h) Thioethers and Acetals



1.F9

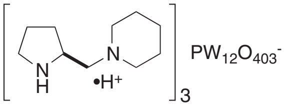


4-MePh 1.F9
2,6-Me_2Ph 38.S31

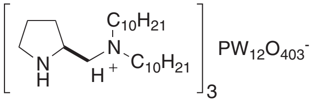


·4-CF_3-Ph-COOH
24.F40
38.S11

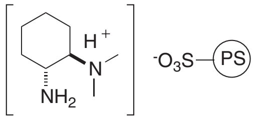
i) Onium Salts



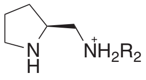
28.T10



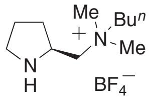
28.T10



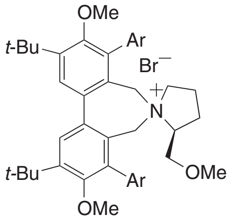
28.T10



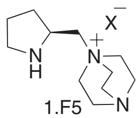
1.F1; 2



22.F6

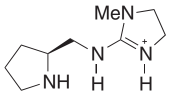


43.S27



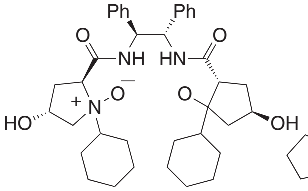
1.F5
22.F6

R = H, X = C, n = 1 1.F5
R = H, X = O, n = 1 1.F5
34.S1
R = Me, X = C, n = 0 31.S4.12

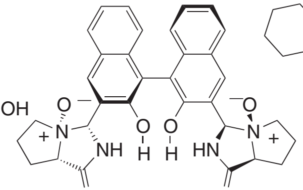


1.F8

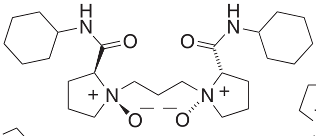
j) N-*Oxides*



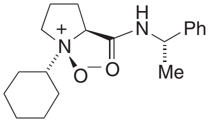
30.T8



30.T7

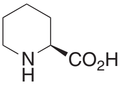


15.S21
30.S3

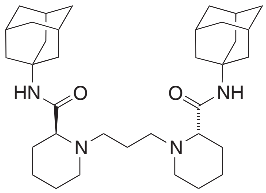


15.F2

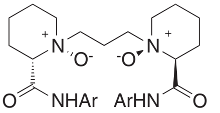
k) Piperazine Derivatives



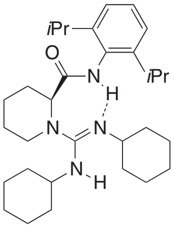
36.S21



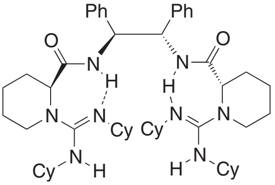
15.S24
30.S15



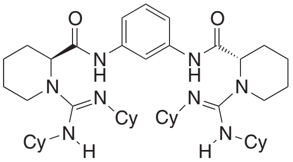
Ar= 2,4,6-$Pr^iC_2H_5$
27.F6



10.S46

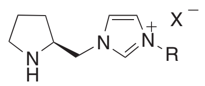


Cy: cyclohexyl
10.S47

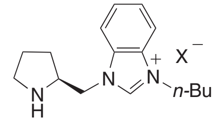


Cy: cyclohexyl
10.S48

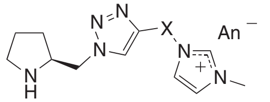
l) Ionic Liquid Tagged Proline Derivatives



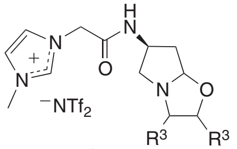
R = *n*-Bu, X = Br or BF_4 1.F6 22.S28
R = *n*-Bu, X=BF_4 16.S50
R = Me, X = Br 22.S28
R = Et, X = Br 22.S28
R = *n*-Bu, X = O_3SO-$C_{12}H_{25}$-*n* 22.S28



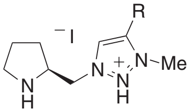
X = Br or $C_{12}H_{25}SO_3$ 1.F6
X=DBSH 24.F23
X=Br 26.S6
22.F6; S29



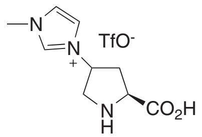
X = -*p*-$C_6H_4CH_2$-, An = BF_4 22.F7
X = -CH_2-, An = Cl 22.F7



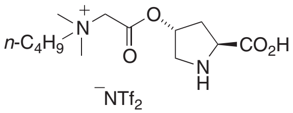
22.S18



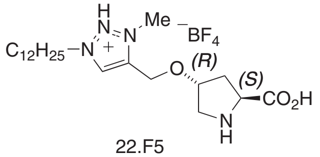
R = Ph or *n*-Bu
22.F5



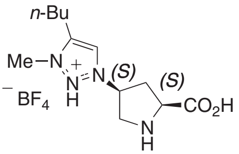
R 27.F2
S 22.S22; 23



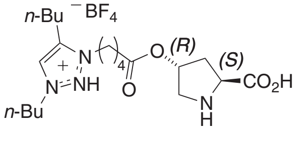
22.S19



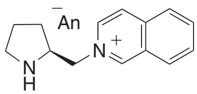
22.F5



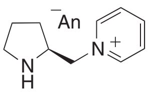
22.F5



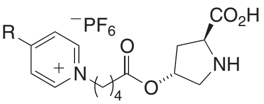
22.F5



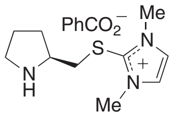
An = Br or PF_6
22.F5



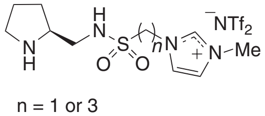
An = Cl or BF_4
22.F5



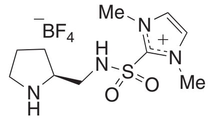
R = CH(*n*-Bu)$_2$ or H
22.S21



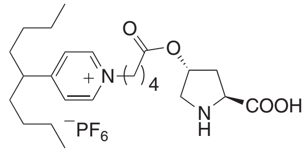
22.F8



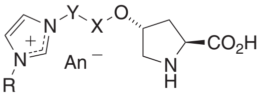
n = 1 or 3
22.F8



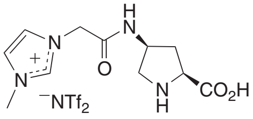
22.F8



24.F10

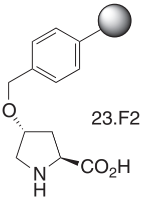


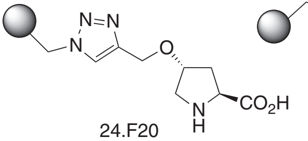
R, R = Me, X = CO, Y = CH_2, An = BF_4 or NTf_2 22.S19
R, R = Me, X = Y = CH_2, An = Br 22.S19
R, R = Me, X = CO, Y = CH_2, An = NTf_2 24.F10
R, R = *n*-$C_{12}H_{25}$, X = CO, Y = $(CH_2)_4$, An = PF_6 or BF_4 22.S21
R, R = *n*-$C_{12}H_{25}$, X = CO, Y = $(CH_2)_4$, An = PF_6 24.F10
S, R = CH_3, X = CO, Y = CH_2, An = NTf_2 24.F10
28.S33

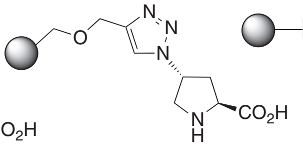


22.S18
24.F10

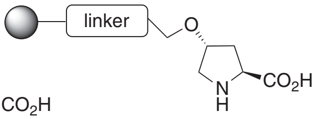
m) Polymer-Supported Prolines/Pyrrolidines


23.F2

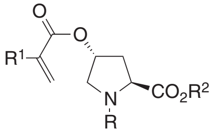

24.F20

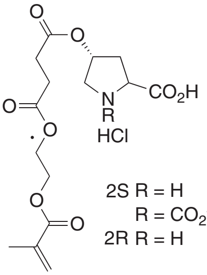


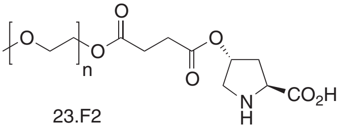
24.F20

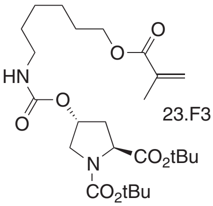


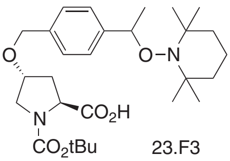
24.F20

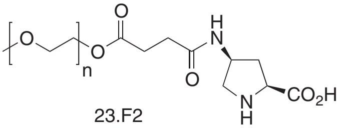

R = H, R^1 = H, R^2 = H (HCl) 23.F3
R = H, R^1 = CH_3, R^2 = H (HCl) 23.F3
R = CO_2tBu, R^1 = CH_3, R^2 = H 23.F3
R = CO_2tBu, R^1 = CH_3, R^2 = tBu 23.F3

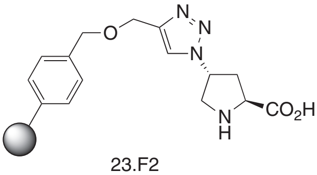

2S R = H 23.F3
R = CO_2tBu 23.F3
2R R = H 23.F3

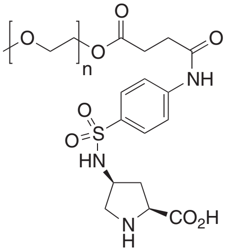

23.F2

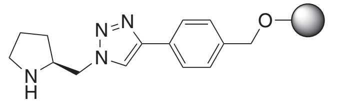

23.F3

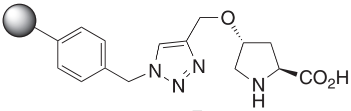

23.F3

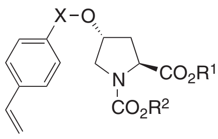

23.F2

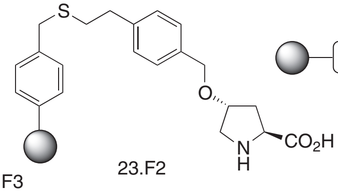

23.F2

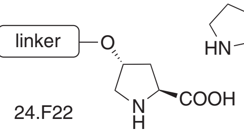

23.F2


24.F23

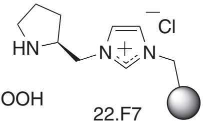

23.F2


X = CH_2, R^1 = H, R^2 = tBu 23.F3
X = CH_2, R^1 = Bn, R^2 = Bn 23.F3
X = CO, R^1 = Bn, R^2 = Bn 23.F3

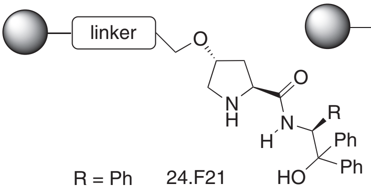

23.F2



24.F22

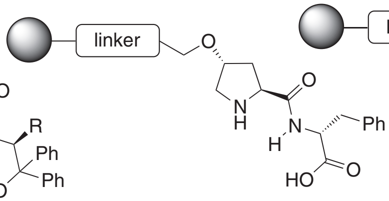

22.F7

n) Polymer-Supported Prolinamides

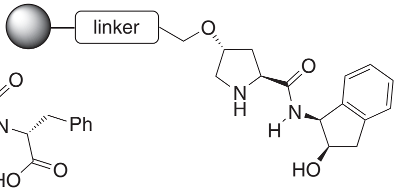


R = Ph 24.F21

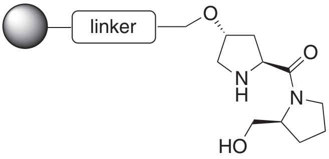
R = *i*Bu 24.F21



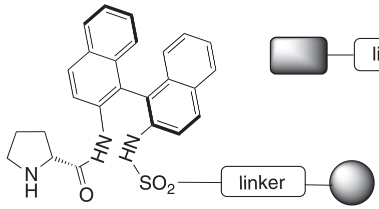
24.F21



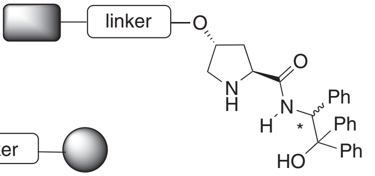
24.F21



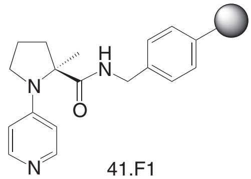
24.F29



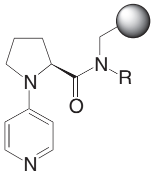
24.F22



24.F22

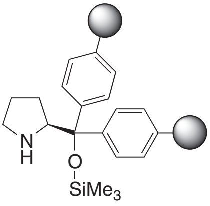


41.F1

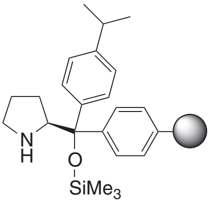


41.F1

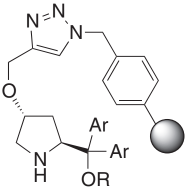
o) Polymer-Supported Diarylprolinols



23.F5



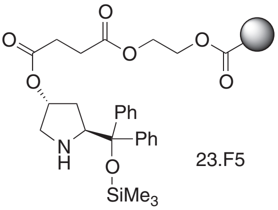
23.F5



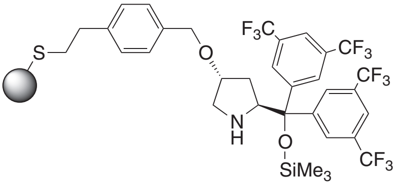
R = TMS, Ar = Ph 23.F5

R = TMS, Ar = 3,5-$(CF_3)_2$-Ph 23.F5

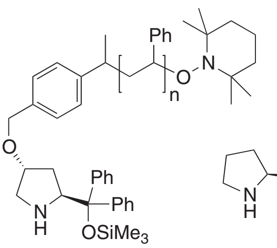
R = CH_3, Ar = Ph 23.F5



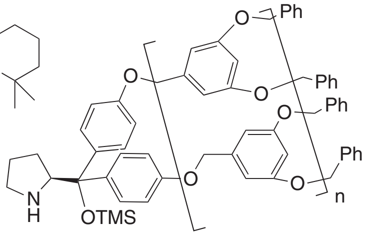
23.F5



23.F5

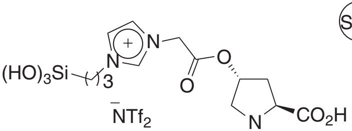


23.F5

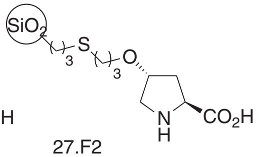


37.S14

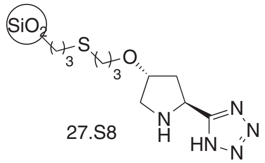
p) Silica-Supported Derivatives



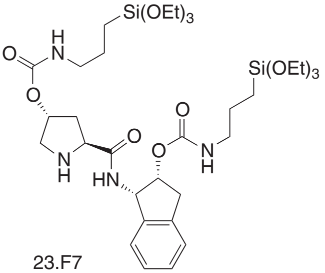
24.F10
22.S21



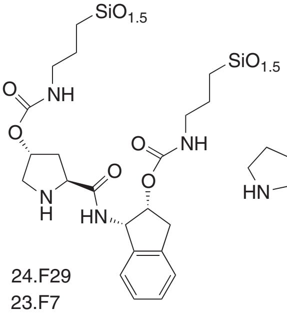
27.F2



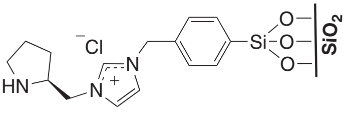
27.S8



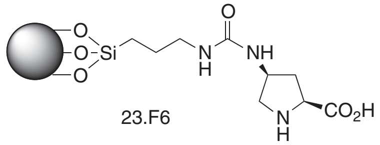
23.F7



24.F29
23.F7

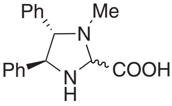


22.F7

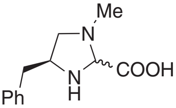


23.F6

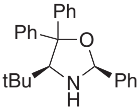
q) Proline Analogs



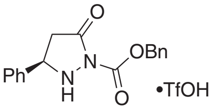
33.S27



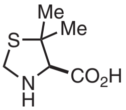
33.S26



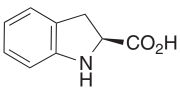
38.S5



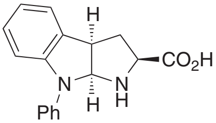
38.S6



42.S5



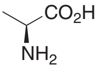
37.S13

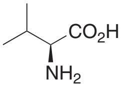


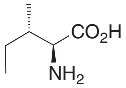
24.F30

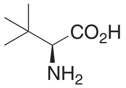
Non-Proline Amino Acids

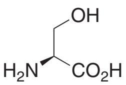
a) Unmodified α-Amino Acids

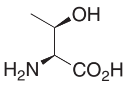

L-Ala:
3.S3; S4

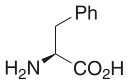

L-Val:
3.S3; S4

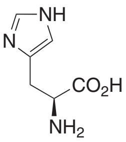

L-*i*-Leu:
3.S3

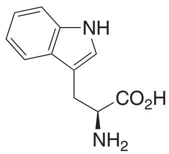

L-*tert*-Leu:
3.S3

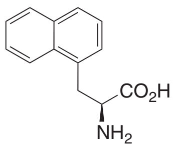

L-Ser:
3.S7

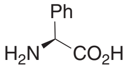

L-Thr:
3.S7

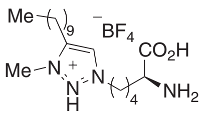

L-Phe:
21.S8; 28
22.S7

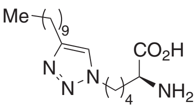

L-His:
3.S3; S6

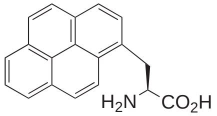

L-Trp:
3.S3; S5
24.F3


3.S3; 19

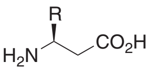

L-Phe-Gly
9.F4


22.S24

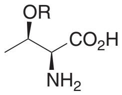

22.S24

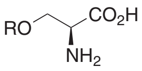

Ala(1-Pyn)
5.S13

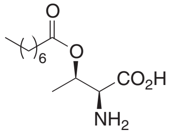
β-Amino acids:

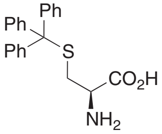

R = Me
R = *i*-Pr
R = Ph
3.S3;13

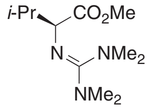
b) Protected Amino Acids

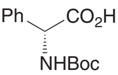

R = TBS: 3.S3; 11, 24.F3
R = TBDPS: 3.S3; 11
R = TIPS: 3.S3
R = *t*-Bu: 3.S3; 8; 12,
28.T1; 5; S6

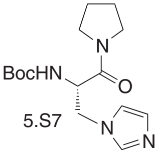

R = TBS: 3.S7
R = TBDPS: 3.S7, 24.F3
R = TIPS: 3.S7
R = $C_5H_{11}CO$: 24.F3


3.S3

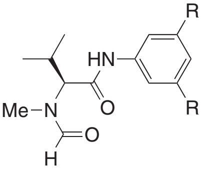

3.S3; 14

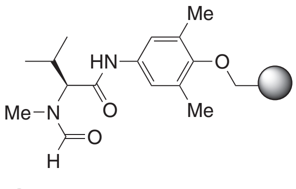

31.S4.13

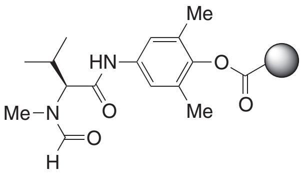

3.S18
6.S61


5.S7

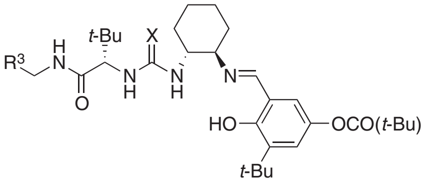
c) N-*Aryl Valinamide Derivatives*


R = Me: 15.F5
R = *t*-Bu: 15.F5; 26
R = Ph: 15.F5
R = 2-MeC_6H_4: 15.F5

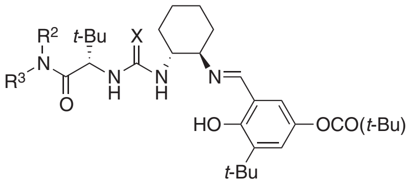

● = insoluble polymer: 15.F7
dendron: 15.F7
Fluorous tag (-CH_2-C_6F_{13}): 15.F7


● = Au nanoparticle: 15.F7
soluble polymer: 15.F7

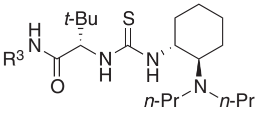
d) (Thio)ureas



R^3 = polystyrene, X = S: 30.S5
R^3 = Ph, X = O: 30.S5; 6; 7

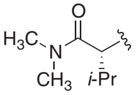


R^2 = H, R^3 = Bn, X = 0: 30.S7
R^2 = Me, R^3 = Me, X = S: 30.S7; 112; T5

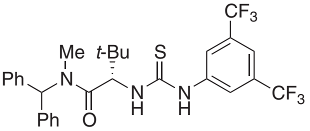


R^3 = CH$_3$: 30.T2
R^3 = *i*-Pr: 30.T2

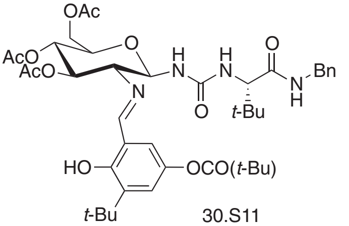
R^3 =



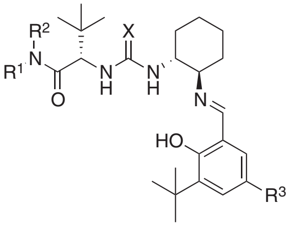
: 29.T2

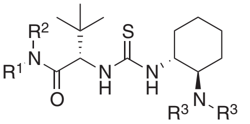


30.S8; T4

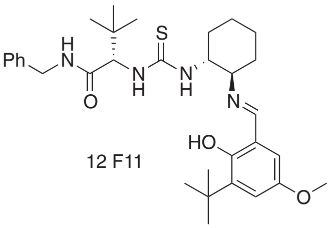


30.S11



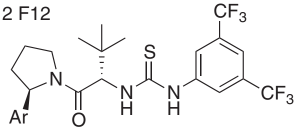


12 F11

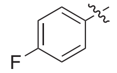


R^1 = Me, R^2 = Me, R^3 = OCO*t*Bu, X = S 12 F12
R^1 = Bn, R^2 = Me, R^3 = *t*Bu, X = S 12 F12
R^1 = Bn, R^2 = H, R^3 = OCO*t*Bu, X = O 12 F12
R^1 = Bn, R^2 = Me, R^3 = OCO*t*Bu, X = S 12 F12; S3

R^1 = H, R^2 = Me, R^3 = *n*-Pr 12 F12
R^1 = Bn, R^2 = Me, R^3 = H 12 F12
R^1 = Bn, R^2 = H, R^3 = H 12 F12
R^1 = Bn, R^2 = Me, R^3 = Me 12 F12

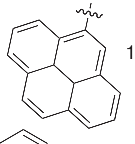


Ar =



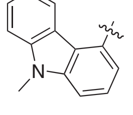
12 F12

Ar =

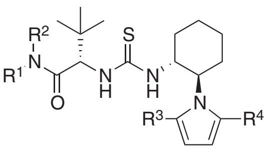


12 F12

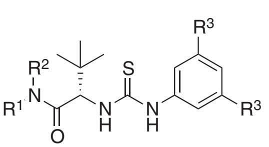
Ar =



12 F12

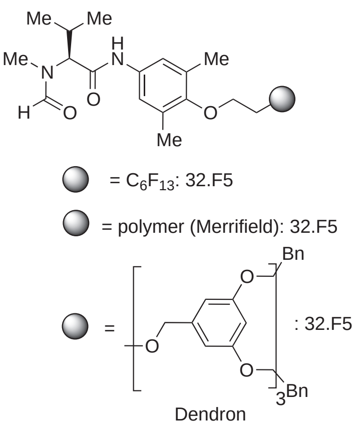


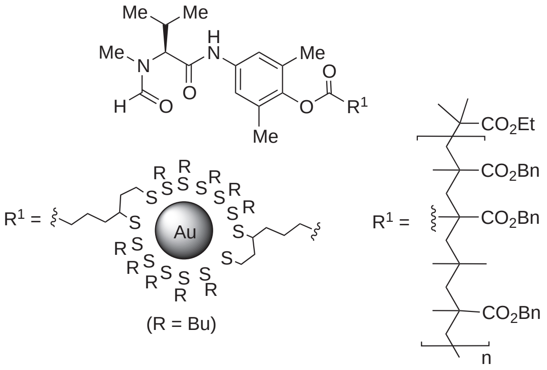
R^1 = *i*-Bu, R^2 = *i*-Bu, R^3 = Me, R^4 = Ph 12 F12
R^1 = *n*-Penthyl, R^2 = Me, R^3 = Me, R^4 = Ph 12 F12
R^1 = Et, R^2 = Et, R^3 = Me, R^4 = Me 12 F12



R^1 = Me, R^2 = CH(Ph)$_2$, R^3 = CF$_3$
R^1 = Me, R^2 = Bn, R^3 = CF$_3$
R^1 = Me, R^2 = Bn, R^3 = H

e) Supported Amino Acids

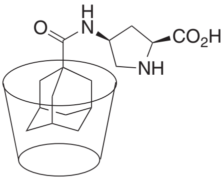




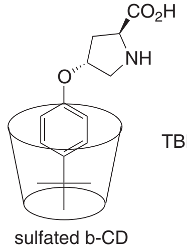
32.F5

32.F5

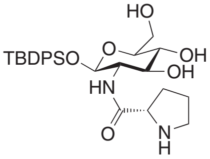
f) Miscellaneous



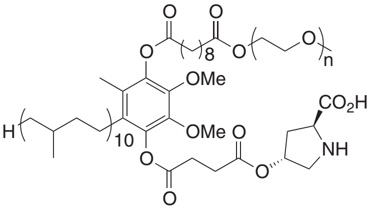
24.F12



24.F12



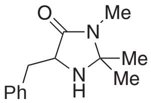
24.F17



24.F17

Chiral Imidazolidinones (MacMillan's Catalysts and Analogs)

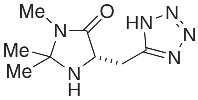
a) "First-Generation" Imidazolidinone Catalysts



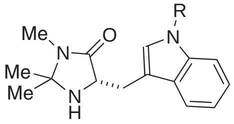
22.S12

R 4.S2; 16; 19; 20; 21; 30; 34
27.S23

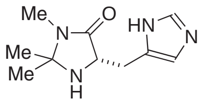
S 2.F2
4.S4, 7, 12, 18 21, 30; 34
24 F38
33.S1; 3; 4; F3
35.S1; 5; 29
36.S3
37.F1
38.S1
39.S2



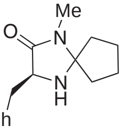
4.S34
38.S6



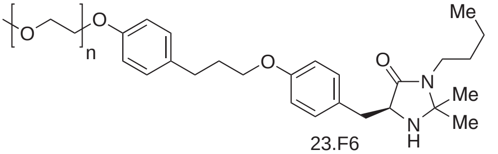
R = Bn 4.S3; 34
33.S16 (HCl)
R = H 33.S16 (HCl)



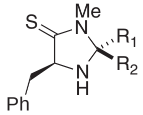
4.S34
24 F40



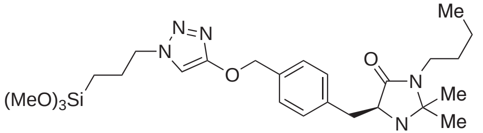
4.S24, 30



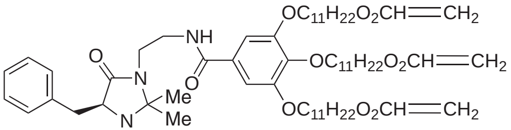
23.F6



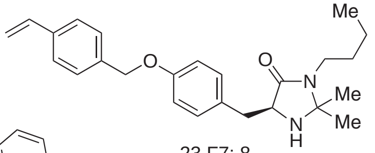
35.S1



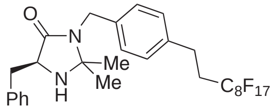
23.F7; 8



23.F7; 8

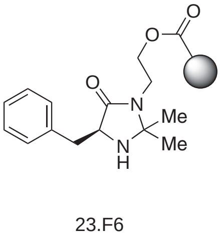


23.F7; 8

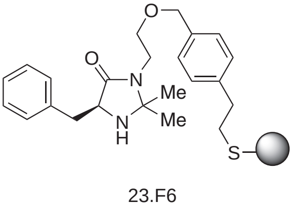


24 F40

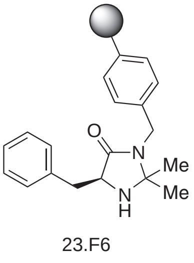
b) Supported "First-Generation" Imidazolidinone Catalysts



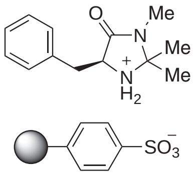
23.F6



23.F6

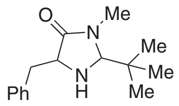


23.F6



23.F6

c) "Second-Generation" Imidazolidinone Catalysts

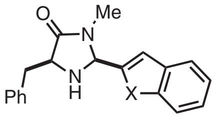


2*S*, 5*S*, 4.S1; 6; 8; 22; 23; 25; 28; 33; 34
21.S8
33.S5; 17; F3
36.S7; 8; 11; 13
35.S1; 5; 20; 27; 28; 30; 31; 33
39.S3; 4; 7; 9; 11; 13; 15; 16

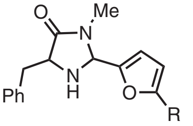
2*R*, 5*R*, 4.S8, 14, 15, 17, 26; 34
27.S17
44.F1

2*R*, 5*S*, 44.F1
39.S3

2*S*, 5*R*, 39.S3



X = S 39.S3; 5
X = O 39.S3; 5; 6; 8

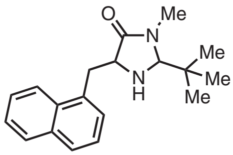


2*S*, 5*S*, R = Me 24 F38
38.S22
39.S3; 5

2*R*, 5*R*, R = Me 33 S39

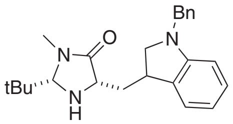
2*S*, 5*S*, R =CF_3 39.S3; 5

2*S*, 5*S*, R = H 35.S1; 27

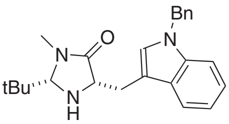


2*S*, 5*S* 35.S1
39.S3; 12; 13

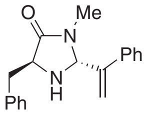
2*R*, 5*R* 36.S12



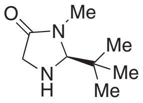
4.S34



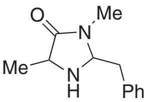
4.S22, 29; 34
35.S1; 19
42.S11
44.F1; S3



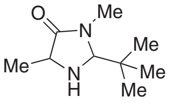
38.F1



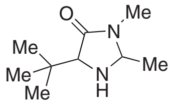
4.S18, 25; 27, 28 30, 31
33.F3; S24
38.S32
44.F1



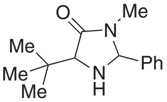
2*R*, 5*S* 39.S20



2*R*, 5*R* 4.S7, 9; 34
2*R*, 5*S* 4.S10; 34
2*S*, 5*S* 4.S34
39.S3; 14



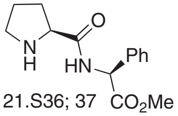
2*S*, 5*S* 39.S3; 18; 19; 21



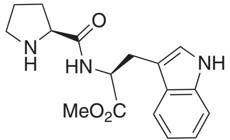
2*S*, 5*S* 4.S13; 34

Di- and Oligopeptide Catalysts

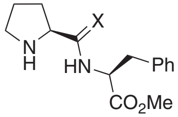
a) Proline-Containing Di- and Oligopeptides



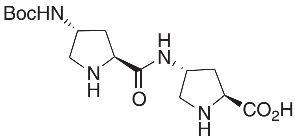
21.S36; 37



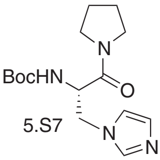
21.S36; 37



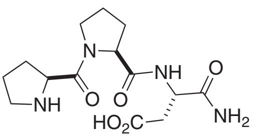
(X = O or S):
21.S35; 36; 37



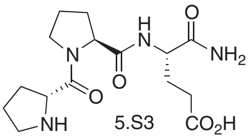
5.S2



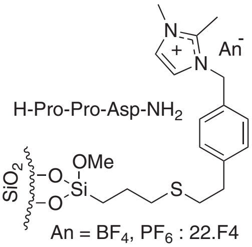
5.S7



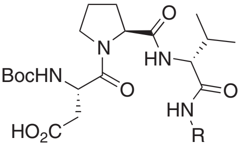
Free: 28.S32; 34
(with TFA): 5.S1



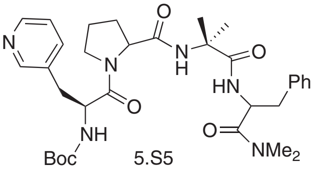
5.S3



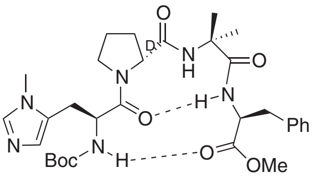
An = BF_4, PF_6 : 22.F4



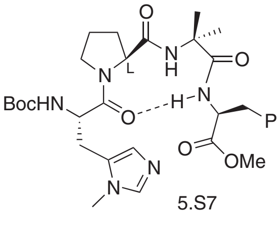
NHR = Ile-Val-OMe : 5.S11
NHR = (*S*)-1-Phenylethylamine : 5.S11
NHR = (*R*)-1-Phenylethylamine : 19.S12; 14



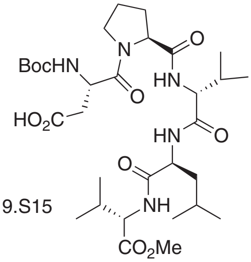
5.S5



5.S7



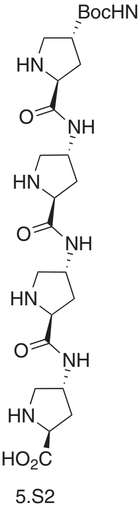
5.S7



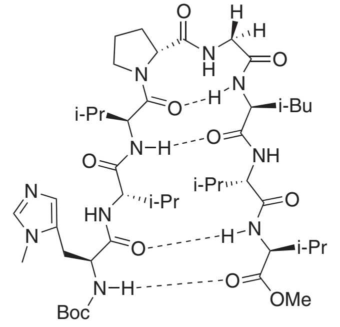
19.S15

Pro-Ach-(Ala(1-Pyn))$_3$-(Leu)$_{28.6}$: 5.S13

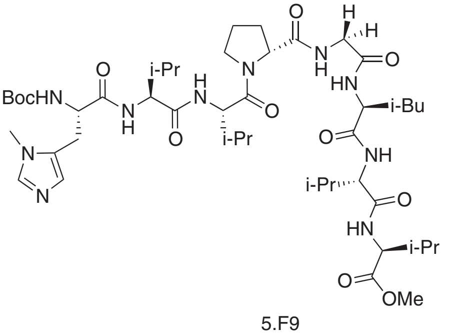
Pro-D-Pro-Aib-Trp-Trp-(Leu)$_{25.4}$: 5.S12



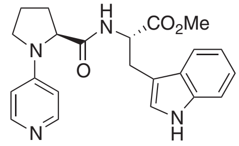
5.S2



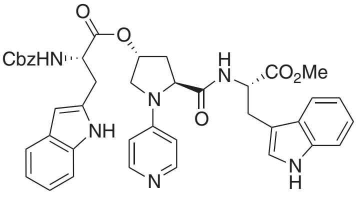
5.F9



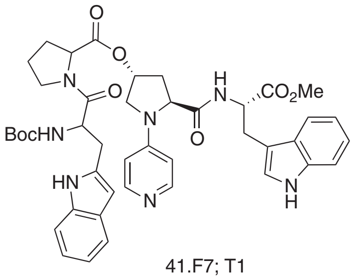
5.F9



41.F7; T1

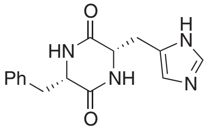


41.F7; T1

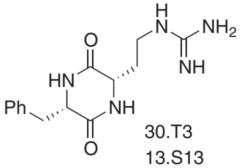


41.F7; T1

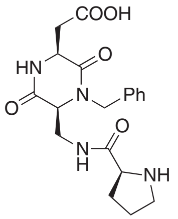
b) Cyclic Dipeptides



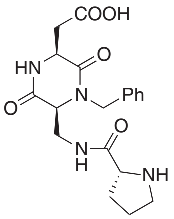
5.S6, 13.S13
30.S1; T1



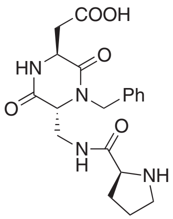
30.T3
13.S13



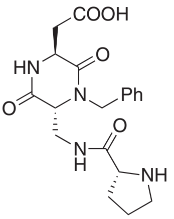
"*cis*"-DKP-L-Pro:
5.S4



"*cis*"-DKP-D-Pro:
5.S4

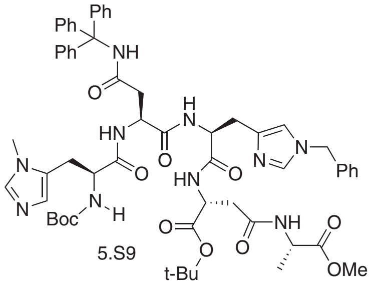


"*trans*"-DKP-L-Pro:
5.S4

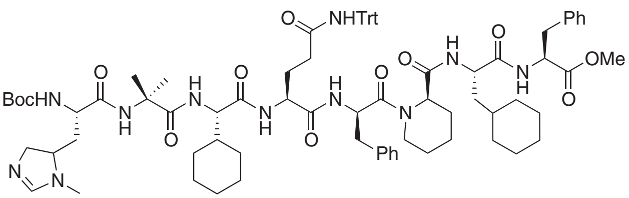


"*trans*"-DKP-D-Pro:
5.S4

c) Non-Proline Oligopeptides



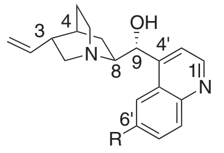
5.S9



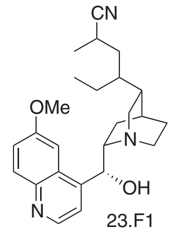
5.T1

Cinchonas

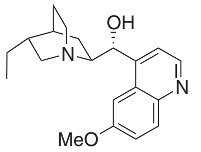
a) Cinchonidine, Quinine, Cupreine, Quinidine, Cinchonine and Cupreidine Derivatives



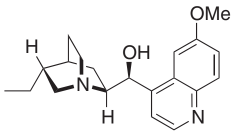
R = H cinchonidine: 6.S1, 13.F3
R = OMe quinine: 6.S3 ;5, 24.F35, 30.T10, 31.F4.3
R = OH cupreine: 6.S10; 11; 12



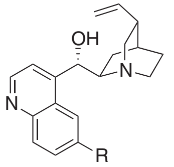
23.F1



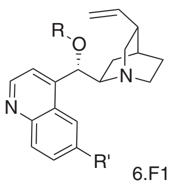
dihydroquinine : 6.S7; 8



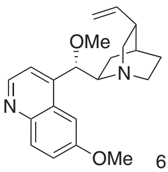
dihydroquinidine : 13.S5



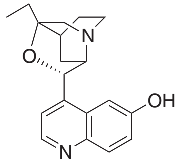
R = OMe quinidine : 6.S2; 4; 6; 21.S2; 4; 39
R = H cinchonine : 13.F3; S2; 30 .S4.11
R = OH cupreidine : 6.S9



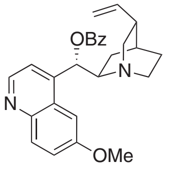
6.F1



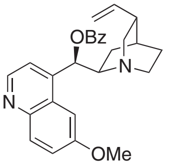
6.S13



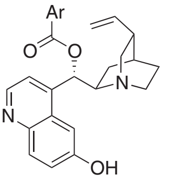
31.S4.4; 7; 8; 9; 10



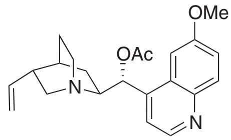
6.S26



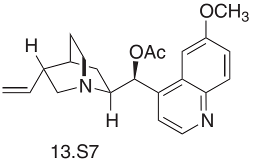
27.F6



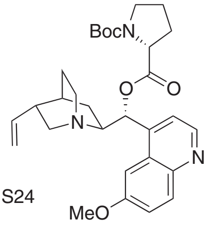
Ar = 3,5-$(CF_3)2C_6H_3$: 6.S27



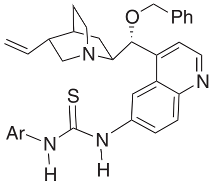
6.S25



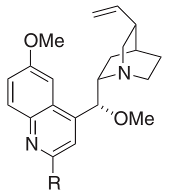
13.S7



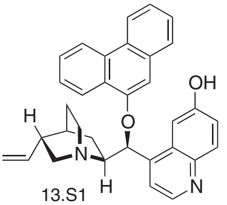
27.S24



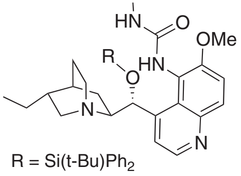
Ar = 3,5-$(CF_3)_2C_6H_3$
6.S30; 31



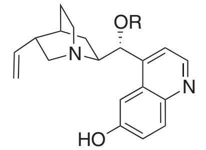
R = Me : 20.T4
R = H: 6.S13, 20.T4; S31



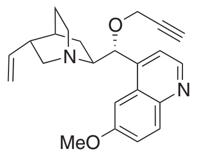
13.S1



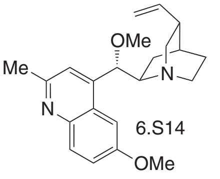
R = Si(t-Bu)Ph_2
Ar = 3,5-$(CF_3)_2C_6H_3$: 6.S64



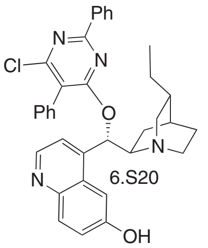
R = *n*-Bu : 6.F5; S21; 23
R = Bn : 6.F5; S21; 23
R = Phenanthryl : 6.F5; S21; 23



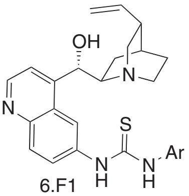
6.S16



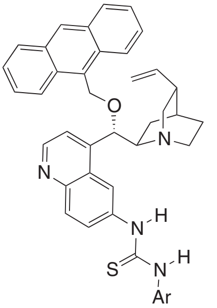
6.S14



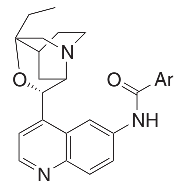
6.S20



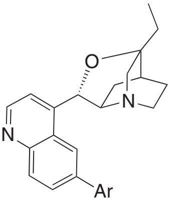
6.F1



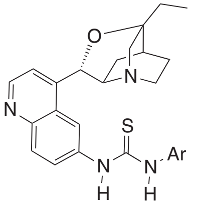
Ar = 3,5-$(CF_3)_2C_6H_3$: 6.S37; 38



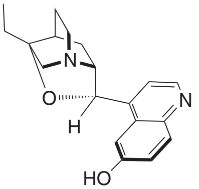
Ar = Ph, 9-anthracenyl: 31.S4; 6



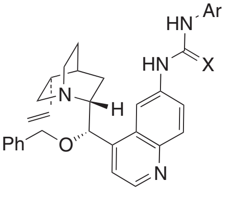
Ar = (biphenyl-4-yl) : 6.S24



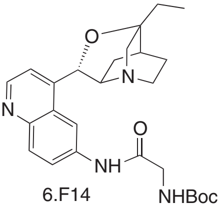
Ar = 3,5-$(CF_3)_2C_6H_3$: 6.S32



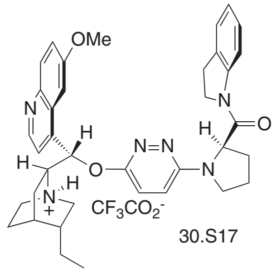
6.F5; S21;23, 13.S3



Ar = 3,5-$(CF_3)_2C_6H_3$: 12.F4

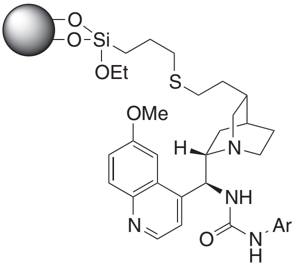


6.F14

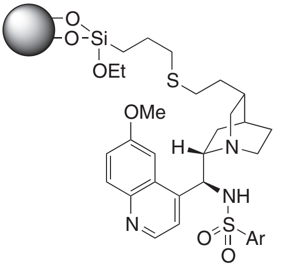


30.S17

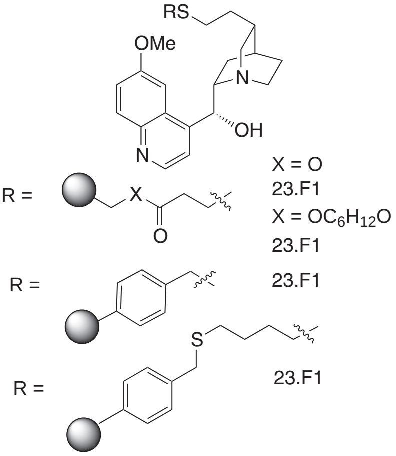
Supported Catalysts



Ar = 3,5-$(CF_3)_2C_6H_3$: 23.F8



Ar = C_6F_5: 23.F8

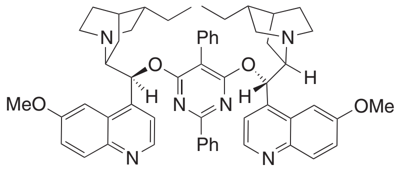


X = O
23.F1
X = $OC_6H_{12}O$
23.F1

23.F1

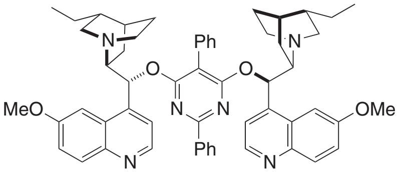
23.F1

Bis-Cinchonas



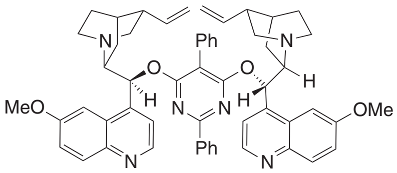
(DHQD)$_2$Pyr

27.S14



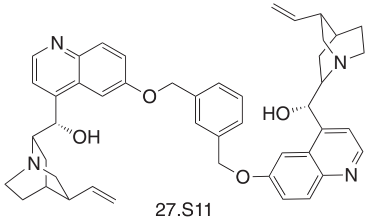
(DHQ)$_2$Pyr

13.S56, 20.T4

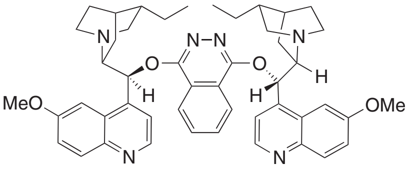


(QD)$_2$Pyr

27.S11

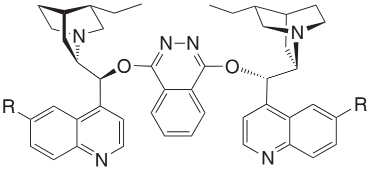


27.S11

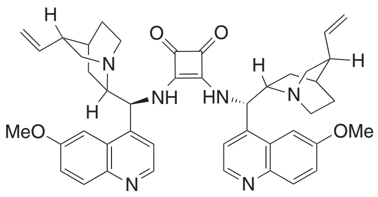


(DHQD)$_2$PHAL

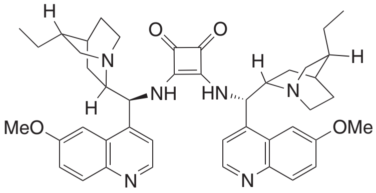
27.S11



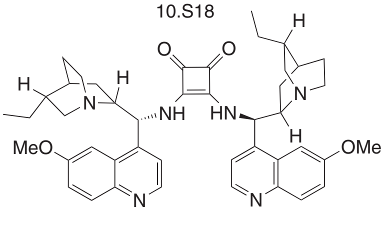
6.F3



10.S18

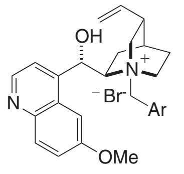


6.S45, 10.S33; 34; 35

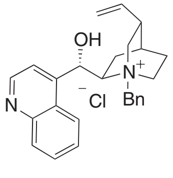


10.S33

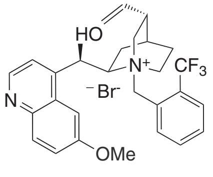
Onium Salts



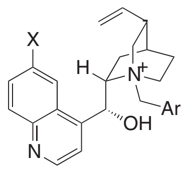
Ar = 2,6-F$_2$-C$_6$H$_3$- : 28.S23



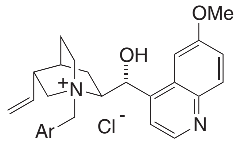
6.S56



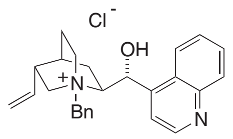
30.S19



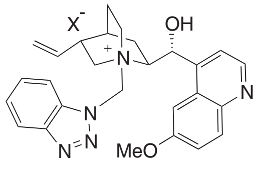
14.S10



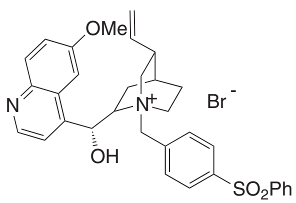
Ar = 2-MeO-C_6H_4: 28.S23
Ar = Ph : 28.S23



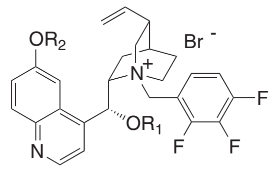
28.S27



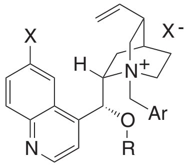
6.S59



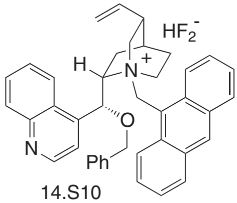
22.S10



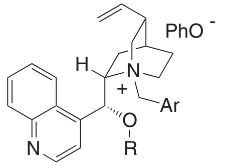
27.S15



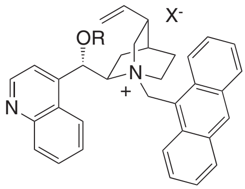
14.S10



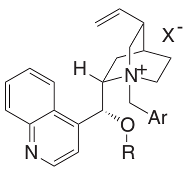
14.S10



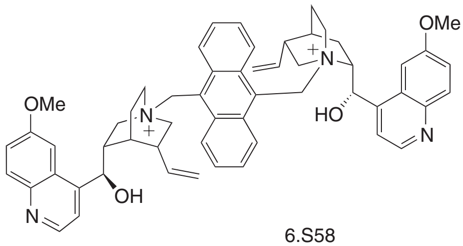
14.S12



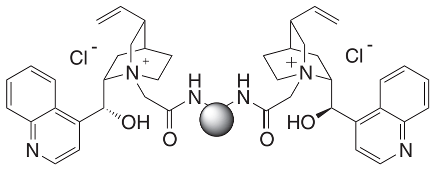
R =CH_2=$CHCH_2$,
X = Br : 27.S3



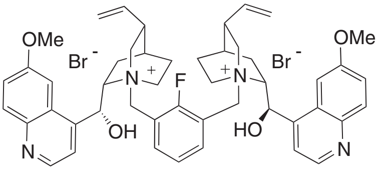
14.S10



6.S58



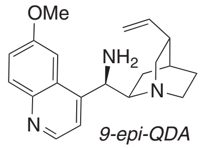
27.S16



6.S57, 65

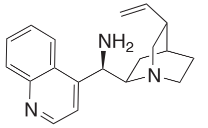
b) 9-Aza-Cinchona Derivatives

The CN-QD Series

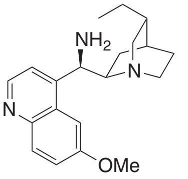


9-epi-QDA

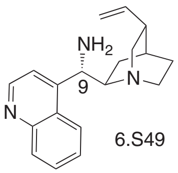
6.S51; 52, 21.S25, 28.S3



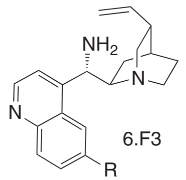
(with BzOH): 21.S10
(with 2 BzOH) : 21.S11; 13; 14
Free: 6.F11, 24.F33



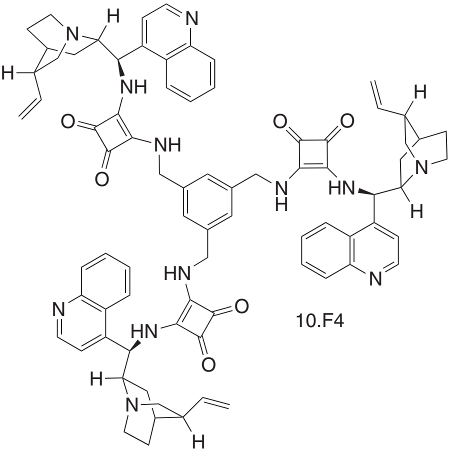
6.S48, 27.F5



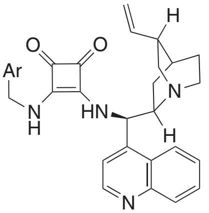
6.S49



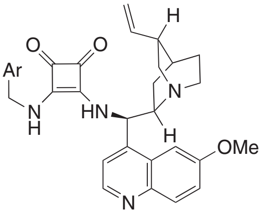
6.F3



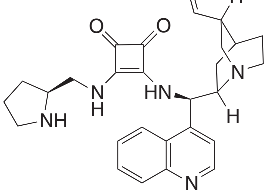
10.F4



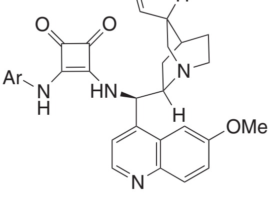
Ar = 3,5-$(CF_3)_2C_6H_3$:
6.S41, 10.F4; 10.S12



Ar = 3,5-$(CF_3)_2C_6H_3$:
10.S40

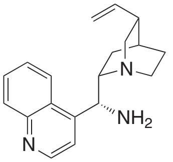


10.F4; 10.S16

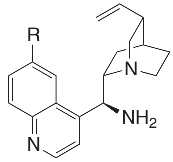


Ar = 3,5-$(CF_3)_2C_6H_3$:
10.S19; 20; 26; 30;
36; 39

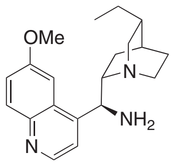
The CD-QN Series



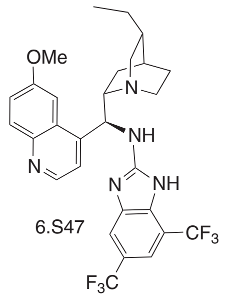
27.S8



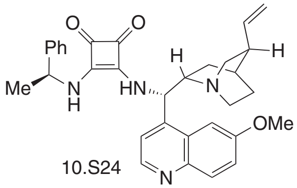
R = OMe: 6.S53, 27.F2, 28.S3
R = H: 6.F11; 12
R = *i*-Pr: 6.S54



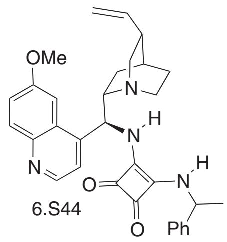
21.S24



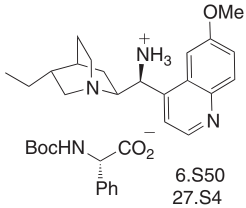
6.S47



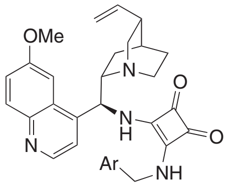
10.S24



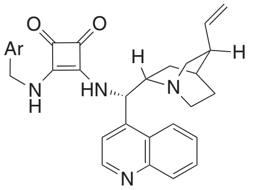
6.S44



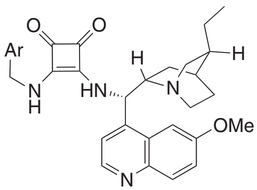
6.S50
27.S4



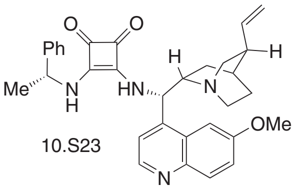
Ar = 3,5-$(CF_3)_2C_6H_3$:
10.S22, 21.S38, 24.F35



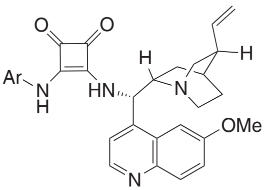
Ar = 3,5-$(CF_3)_2C_6H_3$: 10.S15



Ar = 3,5-$(CF_3)_2C_6H_3$: 10.S33

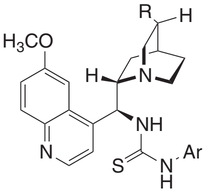


10.S23

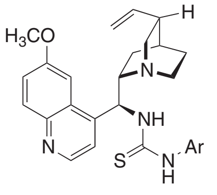


Ar = 4-$(CF_3)C_6H_4$: 10.S21
Ar = 3,5-$(CF_3)_2C_6H_3$:
6.S42; 43, 10.F4, 10.S15
10.S19; 20; 26; 30; 36; 39

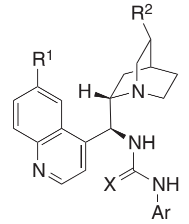
(Thio)ureas



Ar = 3,5-$(CF_3)_2C_6H_3$: 9.F4, 13.S8

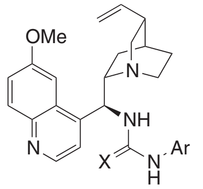


Ar = 3,5-$(CF_3)_2C_6H_3$: 13.S12

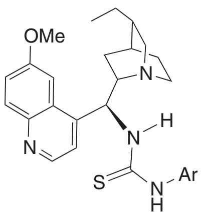


Ar = 3,5-$(CF_3)_2C_6H_3$: 12.F4

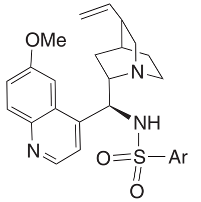
X = S, R^1 = OMe, R^2 = vinyl
X = S, R^1 = OMe, R^2 = ethyl
X = S, R^1 = H, R^2 = vinyl
X = S, R^1 = H, R^2 = ethyl
X = O, R^1 = OMe, R^2 = vinyl
X = O, R^1 = OMe, R^2 = ethyl



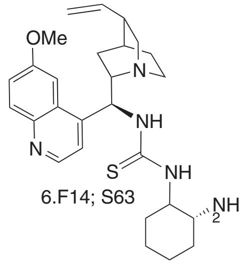
Ar = 3,5-$(CF_3)_2C_6H_3$: 27.S11



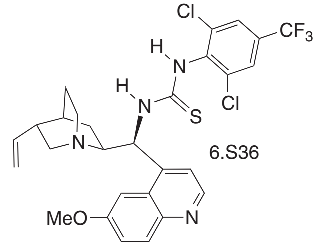
Ar = 3,5-$(CF_3)_2C_6H_3$: 6.S29; 34; 35



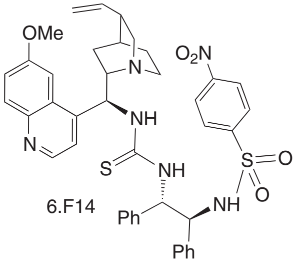
Ar = 3,5-$(CF_3)_2C_6H_3$: 6.S39



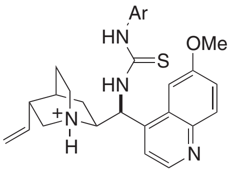
6.F14; S63



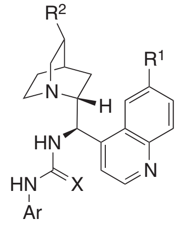
6.S36



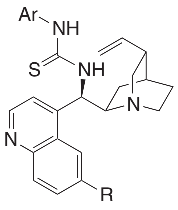
6.F14



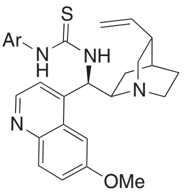
Ar = 3,5-$(CF_3)_2$-C_6H_3
28.F7; S11



Ar = 3,5-$(CF_3)_2C_6H_3$: 12.F4

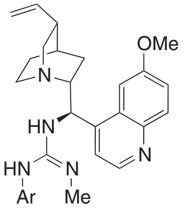


Ar = 3,5-$(CF_3)_2$-C_6H_3 :
R = OMe: 28.S17
R = H: 6.S28; 33

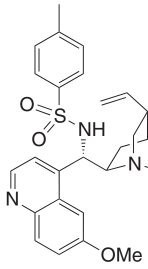


Ar = 3,5-$(CF_3)_2C_6H_3$: 9.F4

Miscellaneous



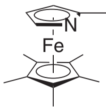
Ar = 3,5-$(CF_3)_2C_6H_3$: 6.S46



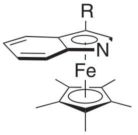
6.S40

Planar Chiral Catalysts

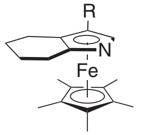
a) Metallocenes



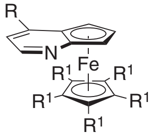
R = TES 8.F5; S2
41.F1
R = Me 8.F5; S2
R = TBS 8.F5; S2
R = TBDPS 8.F5; S2



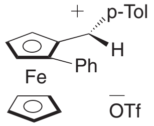
R = H 8.F5
R = N(CH$_3$)$_2$ 8.F5



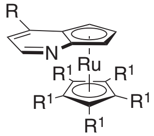
R = H 8.F5
R = N(CH$_3$)$_2$ 8.F5
8.S3



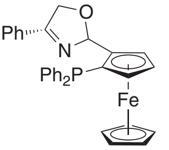
R^1 = Me, R = H 8.F6
R^1 = Me, R = N(CH$_3$)$_2$ 8.F6
R^1 = Ph, R = N(CH$_3$)$_2$ 8.F6
31.S4.11
41.F1
R^1 = Me, R = pyrrolidine 31 .S4.11
40.S3
41.F12; S43
R^1 = Ph, R = pyrrolidin 8.F6
40.S5
41.F11
R^1, R = N(CH$_3$)$_2$ 8.S4
R^1 = 3,5-(CH$_3$)$_2$-Ph, R = pyrrolidine 8.F6
41.S44
R^1 = 3,5-(C$_2$H$_5$)$_2$-Ph, R = pyrrolidine 8.F6



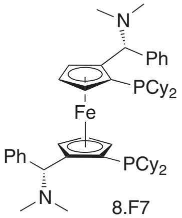
16 S46



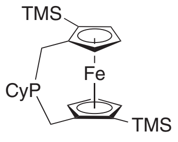
R = N(CH$_3$)$_2$
R^1 = Me 8.F6
R^1 = Ph 8.F6



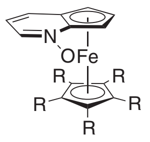
8.F7



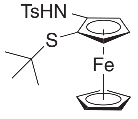
8.F7



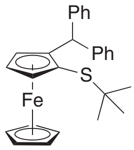
8.F7; S14



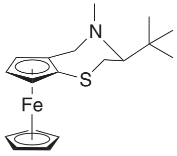
R = Me 8.S11
R = Ph 8.S11
R = 3,5-(C$_2$H$_5$)$_2$-Ph 8.S11
15.F8



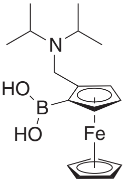
8.F9



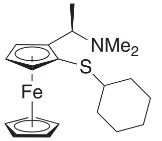
8.F9; S16



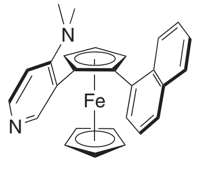
8.F9



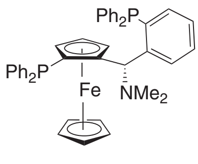
8.S17



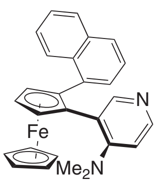
8.F9



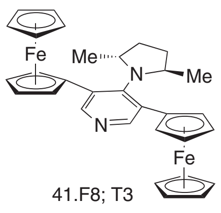
8.S6



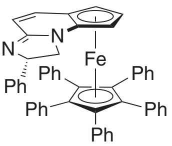
31 .S4.11



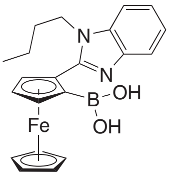
40.S8



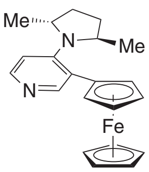
41.F8; T3



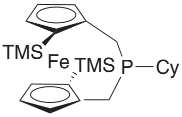
8.S9
41.S13



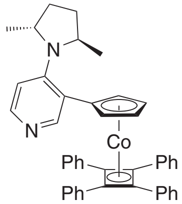
8.S17



41.F8; T3

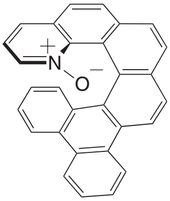


37.F3

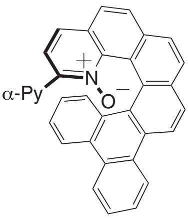


8.S7
40.S6; 7
41.F1; 8; T3

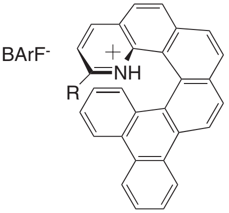
b) Helicenes



15.F8



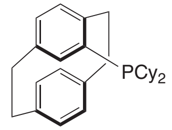
15 F3



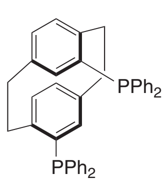
R= 1-adHN-
ad = adamantyl

10.S63, 64

c) Others



8.F7



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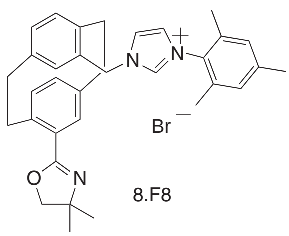

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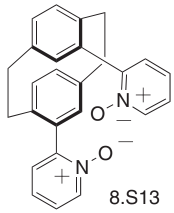
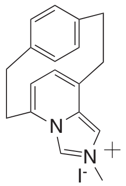
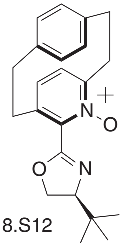


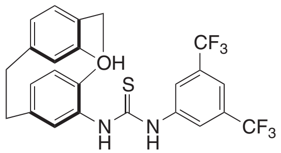
8.S13



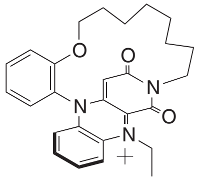
8.F8



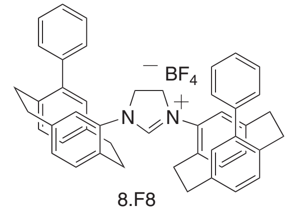
8.S12



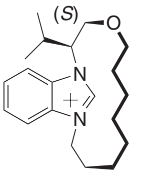
8.S19



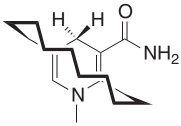
8.F10



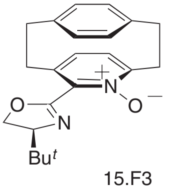
8.F8



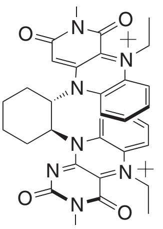
8.S15



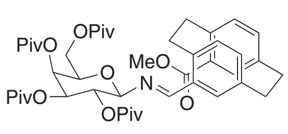
8.S20



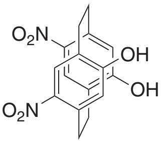
15.F3



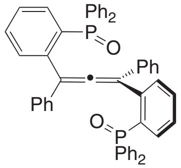
8.F10



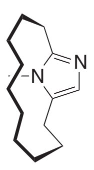
8.S10



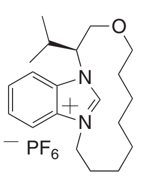
8.S18



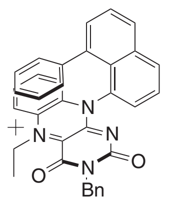
15.F8



8.S8



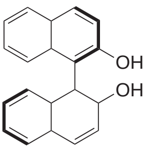
8.F8



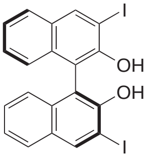
8.F10

Biaryl Catalysts

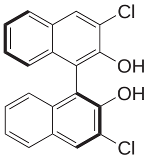
a) Binaphthyl Catalysts



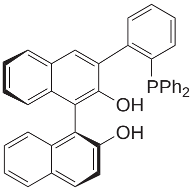
15.S20
43.S3



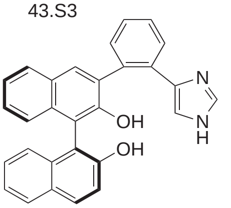
33.S31



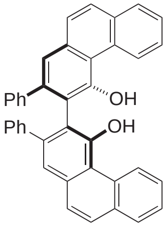
21.S26



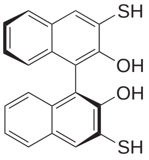
31.S4.20



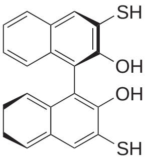
31.S4.14



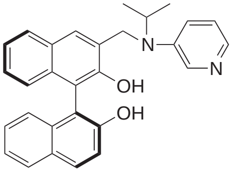
42.F5; S33



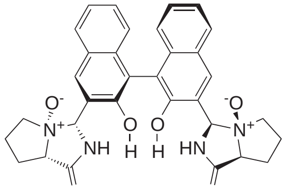
31.S4.35



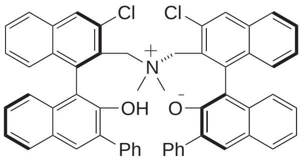
31.S4.35



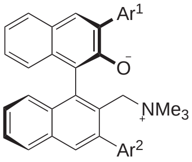
10.S9
31.S4.20; 4.21



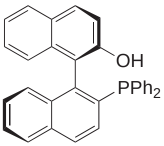
30.T7



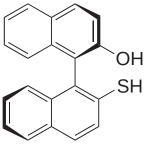
28.S19
29.S2.7



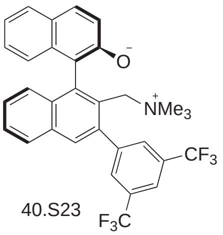
14.S13
Ar^1 = 4-(2,4,6-iPr$_3$C$_6$H$_2$)-C$_6$H$_4$
Ar^2 = Ph 28.S19



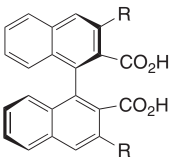
31.S4.7; 4.19; 4.20



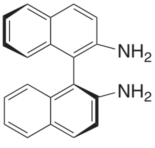
31.S4.35



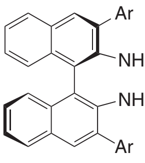
40.S23



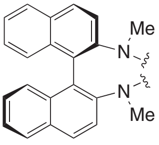
R = H 7.F5
R = 2,6-Me$_{2\text{-}4}$-tBuC$_6$H$_2$ 7.F5; 10.S71
R = 2,4,6-Me$_3$C$_6$H$_2$ 7.F5; 37.F7
R = 2,6-Me$_{2\text{-}4}$-(1-Ad)C$_6$H$_2$ 7.F5
R = SiMePh$_2$ 7.F5; 10.S72
R = CH(2-Np)$_2$ 7.F5; 10.S73
R = CH(9,9-Me$_2$-2-fluorenyl)$_2$ 10.S73



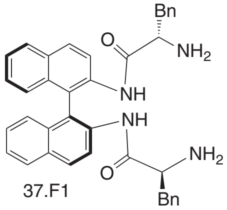
7.S33
38.S18



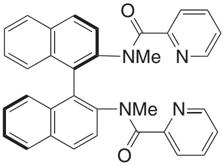
Ar = 3,5-*t*$Bu_2C_6H_3$
7.S34
38.S18



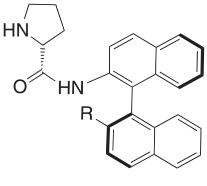
7.F1



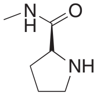
37.F1



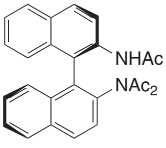
32.F3; T1



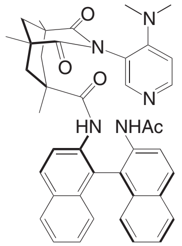
R = -NH-Ms: 24.F22
R = -N$(C_{12}H_{25})_2$: 1.F3
R =



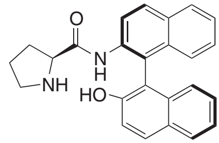
1.F3 24.F16



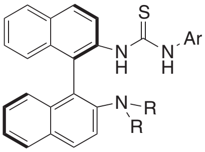
41.F11



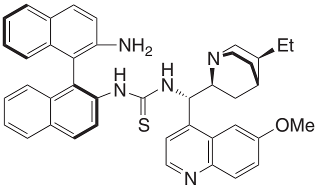
41.F1



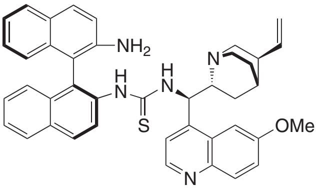
24.F16



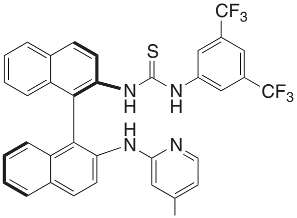
R = Me, Ar = 3,5-$(CF_3)_2C_6H_3$ 12.F10; 13.F6
R = Et, Ar = 3,5-$(CF_3)_2C_6H_3$ 12.F10
R = Me, Ar = 4-Cl-C_6H_4 12.F10
R = H, Ar = 3,5-$(CF_3)_2C_6H_3$ 12.F10; 33.F6; S9



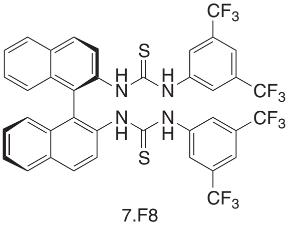
37.S6



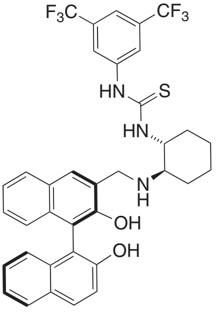
37.S6



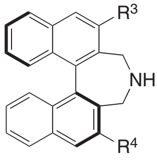
34.S10



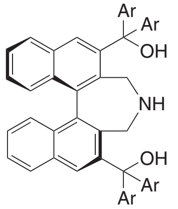
7.F8
35.S2; 35
29.F2.3



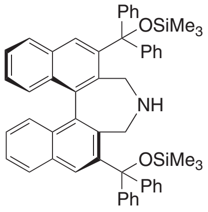
42.F5;
S34
43.S30



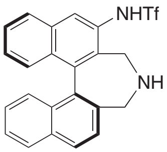
27 S13



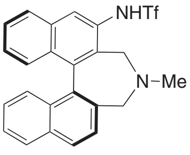
Ar = Ph 7.S29
Ar = C_6F_5 7.S30



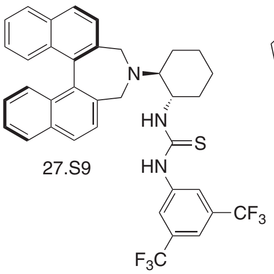
7.S31



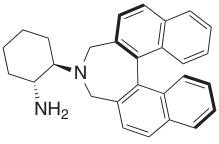
28.T1; 6



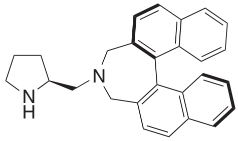
28.F3



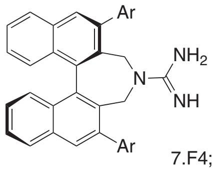
27.S9



24.F5



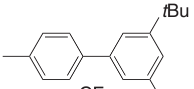
1.F5
24.F25



7.F4; S41; 42

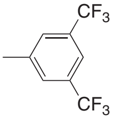
Ar = 4-(3,5-*t*Bu$_2$C$_6$H$_3$)C$_6$H$_4$ 37.F2

Ar:

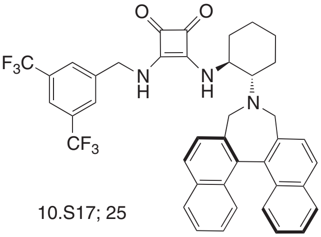


10.S51; 53;
27.S9

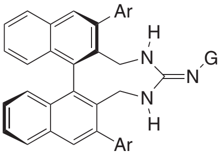
Ar:



10.S52
28.T8

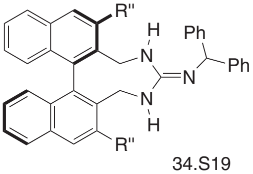


10.S17; 25

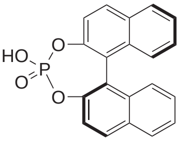


27.S16 34.S19

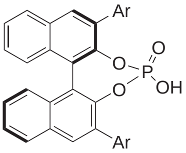
G = Me, Ar = 3,5-(3,5-*t*Bu$_2$C$_6$H$_3$)$_2$C$_6$H$_3$ 7.S35; 40; F4; 10.S54; 13.S14
G = Ph$_2$CH, Ar = 3,5-*t*Bu$_2$C$_6$H$_3$ 7.S36; 7.F4
G = (3,4,5-(MeO)$_3$C$_6$H$_2$)$_2$CH, Ar = Ph 7.S37; 38; 39; F4; 10.S49; 55; 28.T7



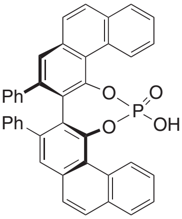
34.S19



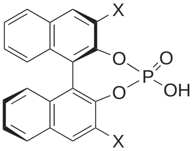
43.S23



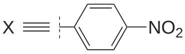
Ar = 4-MeO-C_6H_4
26.S12



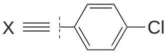
11.S15; 28
32.F2; S5
44.F5



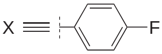
11.S1



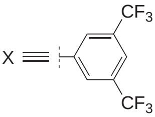
11.S3
43.S22



11.S6; 10b
42.F5; S25; 50



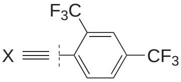
42.F5



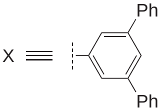
11.S7; 12; 19
32.F2; S1; 10
35.S2; 42.F5; S31

X ≡ Ar = 4-MeO-C_6H_4 26.S12

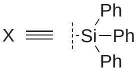
X ≡ Ar =2-MeC_6H_4 32.F2; S34



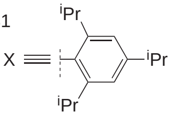
11.S25; 26
35.S2



11.S22

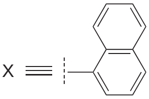


11.S17; 22
26.S10
28.F7; S14
32.F2; S2; 7
35.S2; 9. 18; 26
42.F5; S36

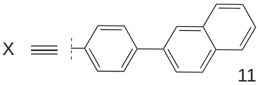


11.S21; 11.F1; 11.S8; 9a;
11, 12; 14; 18; 19; 26; 27;
24.S7; 28.S9; 13; 15; 27;
26.S13; 32.F2; S1; 3; 4; 9;
13; 25; 26; 27; 28; 35.S2;
16; 26; 36.S29; 40.S51;
42.F5; S35; 46; 51; 52
43.S2: 6; 43.S15; 44.F5

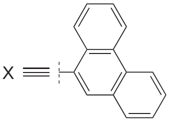
X ≡ Si(*p*-(*t*-Bu)$C_6H_4)_3$ 37.F17



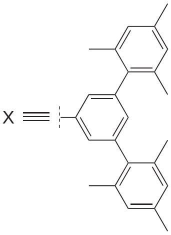
11.S22
32.F2
35.S2

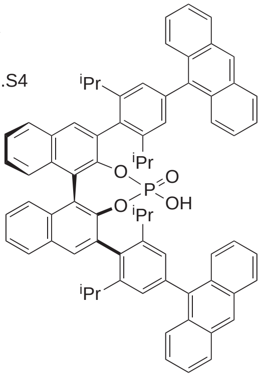


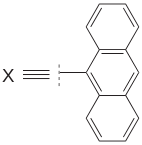
11.S4



11.S16; 20
32.F2; S8; 10; 12;
14; 15; 33; 42.F5S37;
47; 44.F5



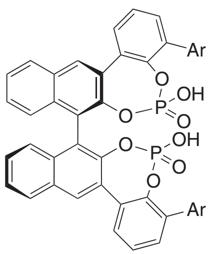




11.S9b; 10a; 15; 24; 25
28.S16;32.F2; S5; 6; 9;
10; 11; 30; 38.S48; 49

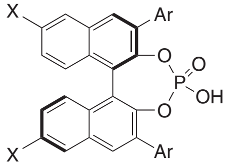
11,F1; 11.S8
42.F5; S30

X ≡ Ph 42.F5

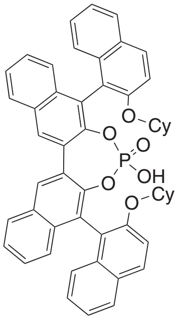


Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$

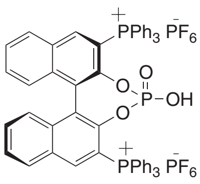
38.S24



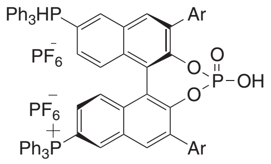
Ar = 2,4,6-iPr$_3$C$_6$H$_2$-, X = H	26.S13 28.F7; S9; 13; 15
Ar = 2,4,6-iPr$_3$C$_6$H$_2$-, X = I	28.F7; S14
Ar = 2,4,6-Me$_3$C$_6$H$_2$-, X = H	28.F7; S14; 35.S2; 15; 42.F5; S26; 35; S31; 41
Ar = 2,6-(iPr)$_2$-4-tBuC$_6$H$_2$-, X = H	33.S35; 40.S46; 44.F5
Ar = 3,5-(Ph)$_2$C$_6$H$_3$-, X = H	35.S2
Ar = 2-Naphtyl-, X = H	37.F2; 42.F5; S45 43.S1; 44.F5
Ar = 2,6-^{i}Pr$_2$-4-(adamant-1-yl)-C$_6$H$_2$-, X = H	44.F5
Ar = 2,6-Me$_2$-4-^{t}BuC$_6$H$_2$, X = H	44.F5
Ar = SiPh$_3$, X = H	26.S10 28.F7; S14



32.F2

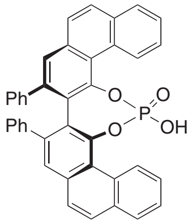


22.S35



Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$

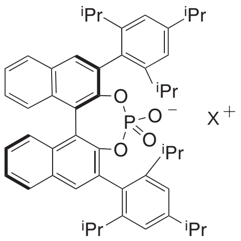
22.S35



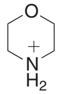
11.S15; 28

32.F2; S5

44.F5

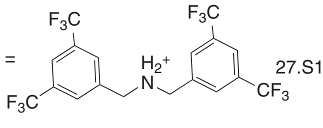


X =

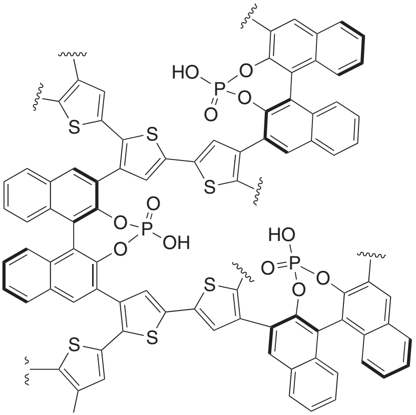


33.F7

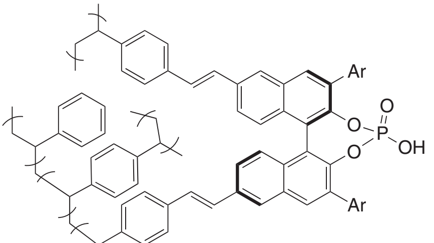
X =



27.S17

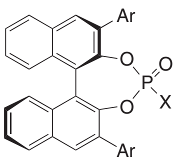


32.S17



Ar = 9-phenylanthryl

32.S16



Ar = 3,5-$(CF_3)_2C_6H_3$

X = OH 7.S53

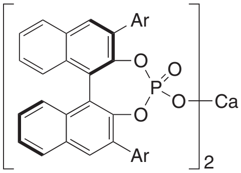
7.S53

X = H; Ar = 4-NO_2-Ph 30.T12

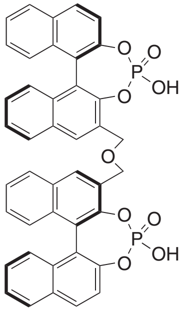
X = TMS; Ar = 4-NO_2-Ph 30.T12

X = H; Ar = 9-phenanthryl 30.S20; T11

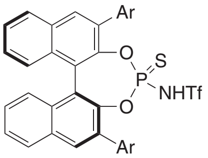
X = $NHSO_2CF_3$



Ar = 4-(β-naphtyl)-C_6H_4
28.S16



42.F5; S44

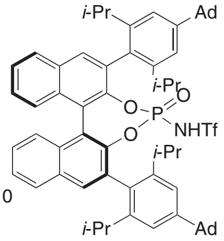


Ar = 2,6-$i\text{Pr}_2$-4-(9-anthryl)-C_6H_2- 28.F7; S10

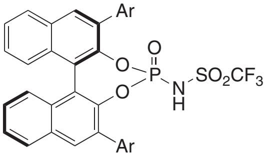
Ar = 4-NO_2-C_6H_4 35.S2

Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$ 35.S2; 15

38.S23

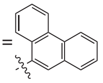


37.F1



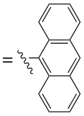
Ar = Ph: 26.S11

Ar =

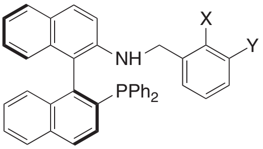


26.S9, 36.S27

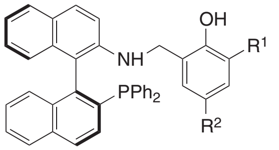
Ar =



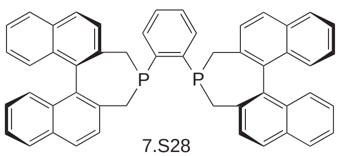
36. S28



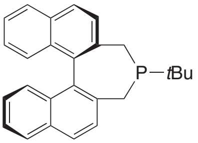
X = H, Y = H 31.S4.17
X = NH_2, Y = H 31.S4.17
X = H, Y = NHTs 31.S4.17
X = NHTs, Y = H 31.S4.17
X = OH, Y = NHTs 31.S4.17



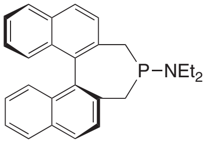
R^1 = H, R^2 = H 31.S4.16; F2.1; S4.15
R^1 = t-Bu, R^2 = H 31.S4.16
R^1 = F, R^2 = H 31.S4.16
R^1 = t-Bu, R^2 = Br 31.S4.16
R^1 = F, R^2 = Br 31.S4.16
R^1 = t-Bu, R^2 = NO_2 31.S4.16



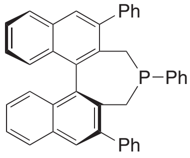
7.S28



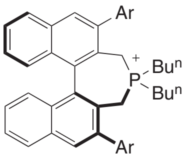
7.S23; 24; 15.S12
37.F3



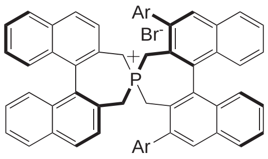
7.S25



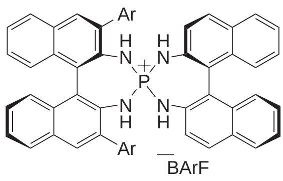
7.S26



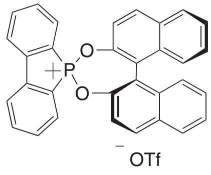
Ar = 3,5-$(CF_3)_2C_6H_3$
27 S9 28.S26



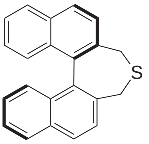
Ar = 3,5-$(CF_3)_2C_6H_3$
27 S12



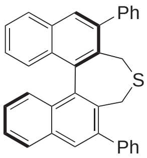
Ar = 3,4,5-$F_3C_6H_2$
7.S58 10.S70 34.S18



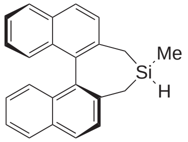
16.S27



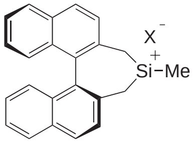
20.S5



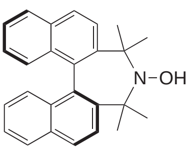
20.9b



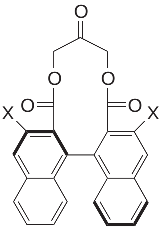
16.S4



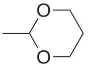
X = TPFPB 16.S3; 5
X = TFPB 16.S3

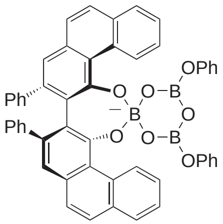


19.F14; S21

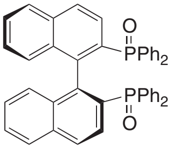


X=H 19.F1; 27 F3

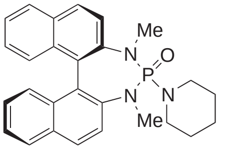
X=  19.F1



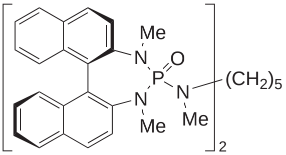
40.S44



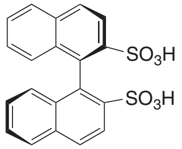
7.S16; 17; 18; 19
15.F3; S5; 15; F8
32.F3; T1



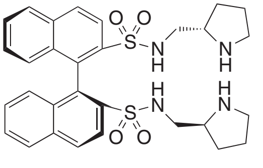
7.S1; 3
15.F8



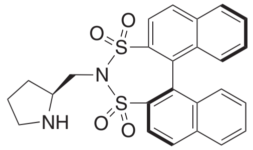
7.S2; 4; 5; 6; 7; 8; 9; 10; 11; 12
15.F4; S17; 18; 22



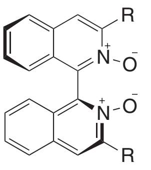
7.S45; 46
28.F7



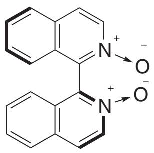
7.S32



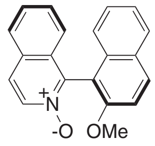
24.F27



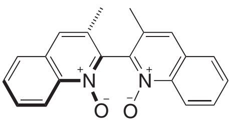
R = H 7.F2, 7.S15; 15.F4; F8
R = Ph 7.F2



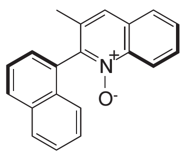
15.F8



15.F2; S4

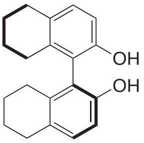


15.F2; S23
7.S14

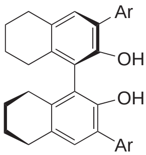


15.F4

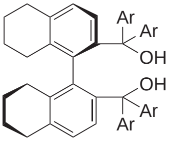
b) Bis-Tetralins



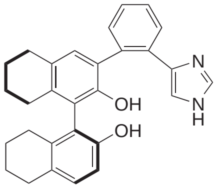
28.F7



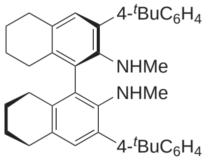
Ar = 3,5-$(CF_3)_2C_6H_3$
7.S43 ; 10.S8
Ar = 3,5-$Me_2C_6H_3$
7.S43 ; 10.S8



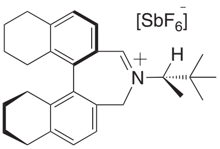
Ar = 4-F-3,5-$Me_2C_6H_2$
7.S44 ; 10.S6; 38.S34
Ar = 4-F-3,5-$Et_2C_6H_2$
7.S44 ; 10.S6; 38.S34



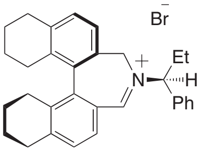
31.S4.14



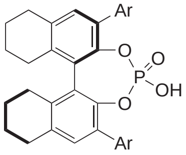
38.S7



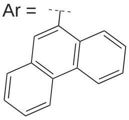
19.S11



19.F10

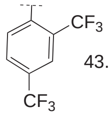


Ar = 2,4,6-$Me_3C_6H_2$- 28.F7; S12
Ar = Ph_3Si 32.F2; S8
Ar = Ph 32.F2; S34; 44.F5
Ar = 4-ClC_6H_4 38.S51; 52
Ar = 2-Naphtyl 35.S2; 40.S43
Ar = 1-Naphtyl 35.S2; 40.S54
Ar =

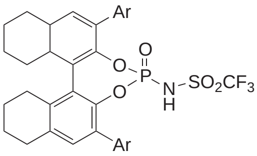


42.F5; S39

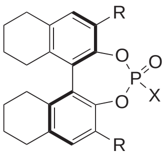
Ar =



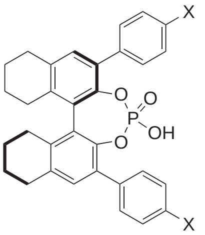
43.S2



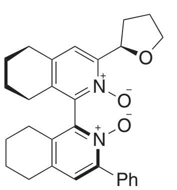
Ar = 2-naphthyl 32.F2; S10
Ar = Ph 36.S30



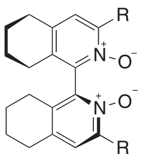
R=$SiPh_3$, X=NHTf 35.S2; 8
R=$SiPh_3$, X=OH 35.S2; 14; 26; 44.F5; 29.F2.3; 29.S2.12; 2.13
R=$CHPh_2$, X=OH 35.S2



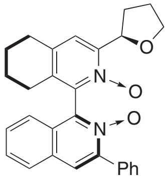
X=H 42.F5; S25
X=F 42.F5; S25; 43
X=Cl 42.F5; S25; 27; 48; 49



15.F2; S6

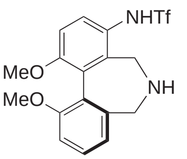


R = Ph 7.F2
R = (*R*)-Tetrahydrofuran-2-yl 7.F2

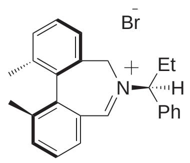


15.F8; S7

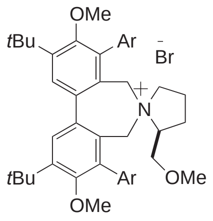
c) Biphenyl/Bipyridyl Catalysts



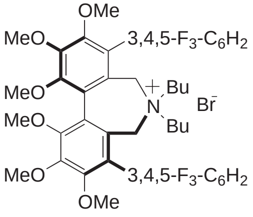
28.T1



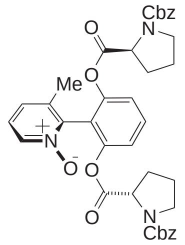
19.F10



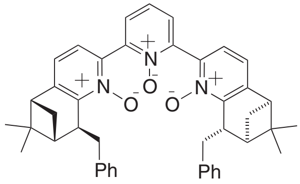
Ar = 3,5-$(CF_3)_2$-C_6H_3-
28.S23
43.S27



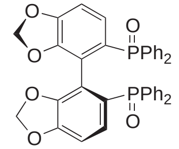
44.F11



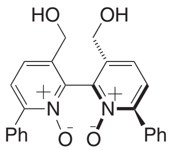
15.F2



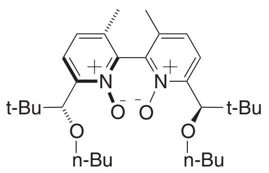
15.F2



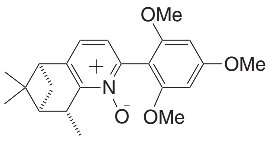
7.S20



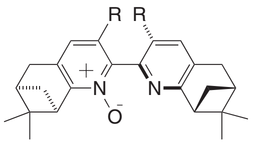
15.F2
7.F2



15.F4; S16
7.S14

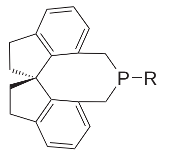


15.F2; S4; S7

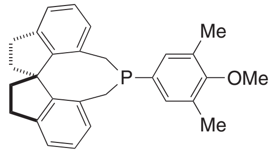


R = H 15.F2 15.F8
R = Me 15.F2 15.F2; S4

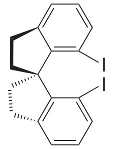
d) Spirobiindanes



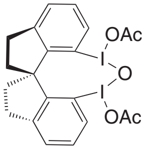
R = Ph 7.S27 36.S23
R = *c*Hex 7.S27



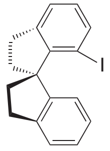
20.S27



19 F11; S16

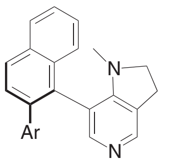


19 F11

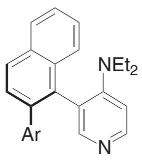


19 F12

e) Miscellaneous



41.F1

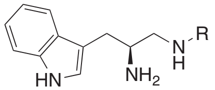


41.F1

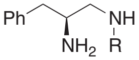
1,2-Diamines

a) α-Amino Acid-Derived Diamines

Primary / Secondary Diamines



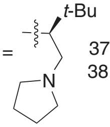
R = Et: 3.S3; S16
R = *n*-Pr: 3.S3; S15
R = *t*-Bu: 3.S3; S15



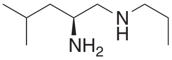
R = *n*-Dec: 3.S3
R = Me: 3.S3
R = *t*-Bu: 3.S3; 18; 20

R = n-Pr 21.S10
R = $C_{10}H_{21}$ 24.F33

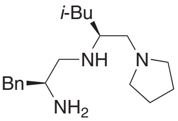
R =



37.F5
38.S21

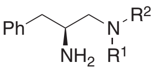


3.S3; S21

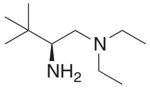


3.S3;22

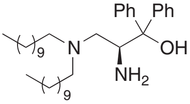
Primary/Tertiary Diamines



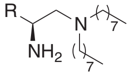
R^1, R^2 = $(CH_2)_4$: 3.S9
R^1 = R^2 = Et: 3.S9



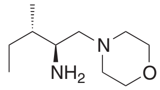
3.S9



3.S9

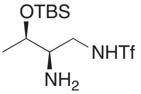


R = *i*-Pr, *s*-Bu;
i-Bu or Bn: 3.S9

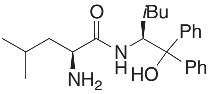


24.F5

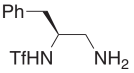
Aminoamides



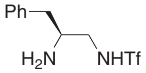
3.S3;17
34.S32



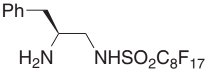
3.S3;10



24.F6

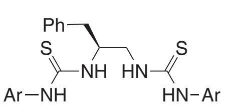


24.F6

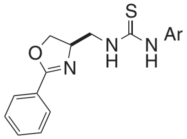


24.F6

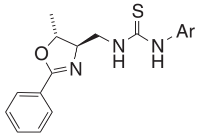
Miscellaneous



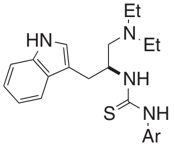
12.F7



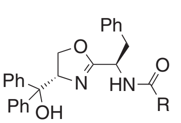
13.F6



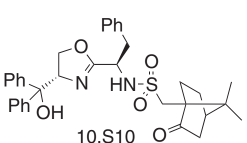
29.F2.2



Ar = 3,5-$(CF_3)_2$-C_6H_3-
28.T7

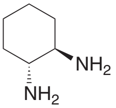


R = CF_3, CCl_3, $CHCl_2$, CH_2F, CH_2Cl
10.S10

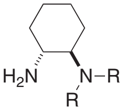


10.S10

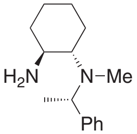
b) 1,2-Diaminocyclohexane Derivatives



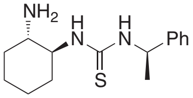
21.S10



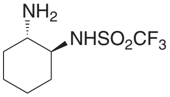
R = Pr: 28.F3; T1; 3
R = nBu: 24.F5; 28.T3



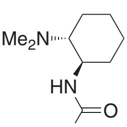
24.F5



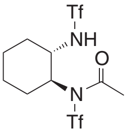
24.F32



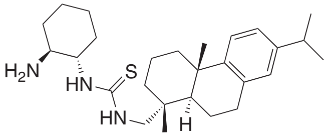
24.F32



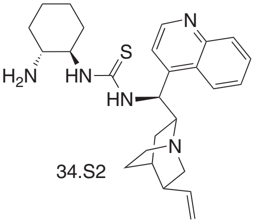
27.S9



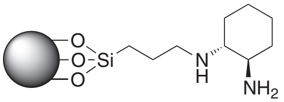
41.F11



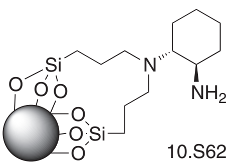
24.S6



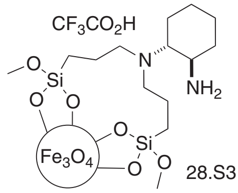
34.S2



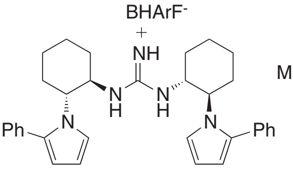
23.F6



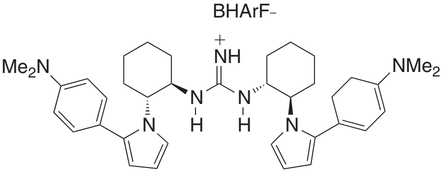
10.S62



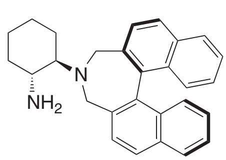
28.S31



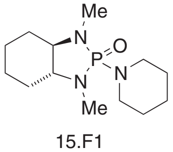
10.S57
40.S37; 38



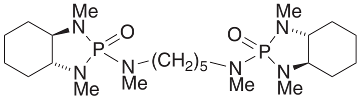
40.S37



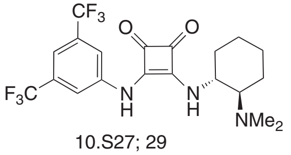
24.F5



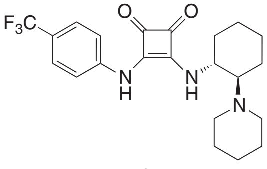
15.F1
16.S15



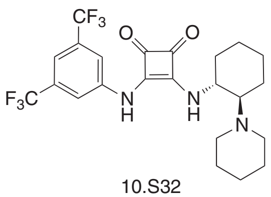
15.F1



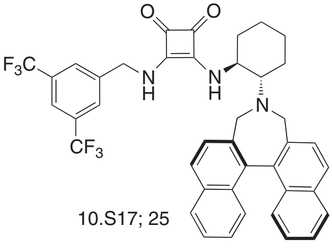
10.S27; 29



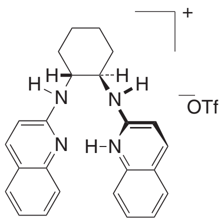
10.S13; 14



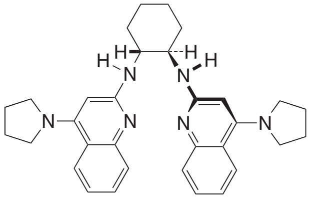
10.S32
27.S9



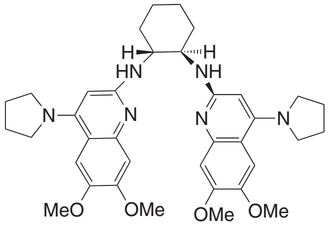
10.S17; 25



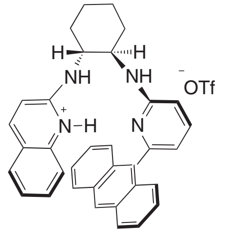
10.S58; 60
29.F2.3
29.S2.11



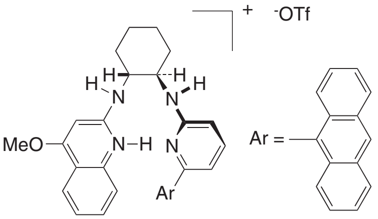
10.S61
29.F2.3



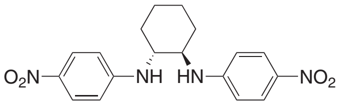
29.S2.8



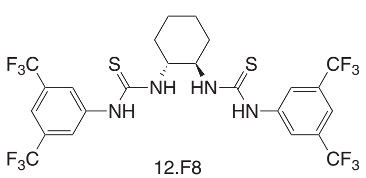
28.F7
29.S2.11; F2.3



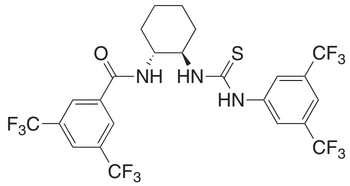
10.S59
29.F2.3



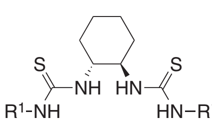
12.F7



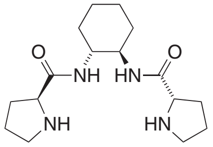
12.F8
38.S22
41.F14; S49



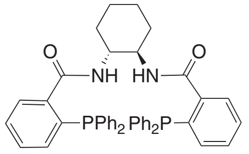
41.F14; S50; 51; 52; 53; 54; 43.S4



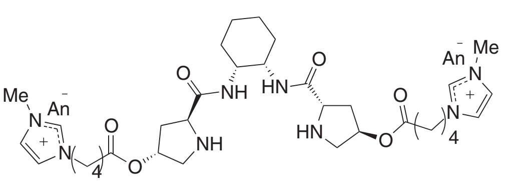
R = Ph 12.F7
R = $(CF_3)_2C_6H_3$ 12.F7



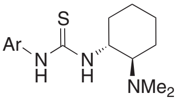
22.S8



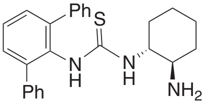
41.S45



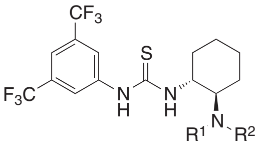
An = Br 22.S25
An = PF_6 22.S25



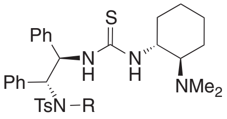
29.F2.2



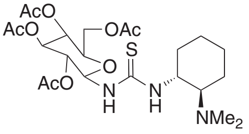
36.S35
43.S25, T1



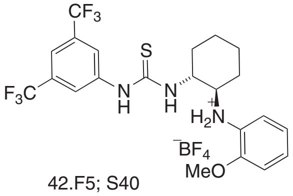
R^1 R^2 = H 24.S8 26.S1434.S3
33.F6; S9 (24.S8 *ent*) 43.T1; S25
R^1 R^2 = Me 12.F2 13.S9; 10, 30.T6 34.S7; 8; 9; 16
31.S4.30, 37.F2; S11 38.S26 44.F7 29.S2.1; 2.2
R^1 = C_2H_4OH; R^2 = Me 42.F5; S32
R^1 = H; R^2 = Bn 32.S29



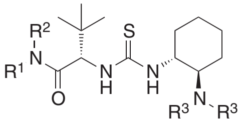
R = Me: 27.S9
R = H: 29.S2.2; F2.2



29.F2.2

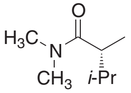


42.F5; S40

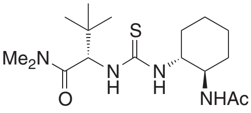


R^1 = H, R^2 = Me, R^3 = *n*-Pr 12.F12
R^1 = Bn, R^2 = Me, R^3 = H 12.F12, 34.S2
R^1 = Bn, R^2 = H, R^3 = H 12.F12, 24.F32, 34.S2
R^1 = Bn, R^2 = Me, R^3 = Me 12.F12
R^1 = CH_3, R^2 = H, R^3 = *n*-Pr 30.T2
R^1 = *i*-Pr, R^2 = H, R^3 = *n*-Pr 30.T2

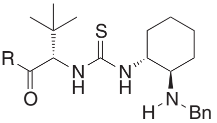
R^1 =



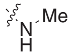
R^2 = H, R^3 = *n*-Pr 30.T2



29.F2.3; S2.9

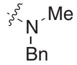


R =



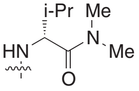
32.S29

R =

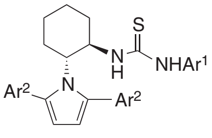


32.S29

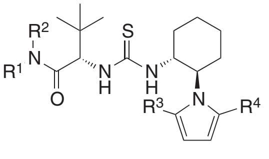
R =



32.S29



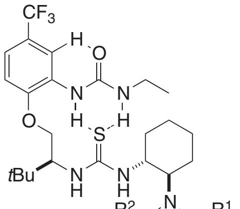
Ar^1 = 3,5-$(CF_3)_2C_6H_3$ 37.F1
Ar^2 = 3,5-$F_2C_6H_3$ 37.F1



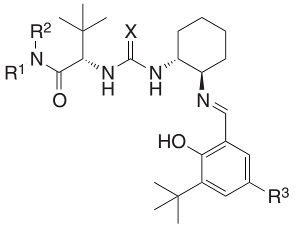
R^1 = *i*-Bu, R^2 = *i*-Bu, R^3 = Me, R^4 = Ph
12.F12, 35.S2; 13; 32, 35.S24, 44.F7

R^1 = *n*-Penthyl, R^2 = Me, R^3 = Me, R^4 = Ph
12.F12, 35.S2; 32, 36.S25, 44.F7

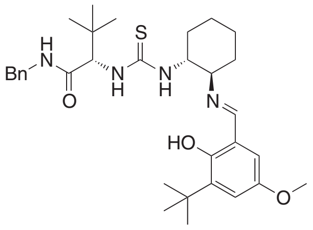
R^1 = Et, R^2 = Et, R^3 = Me, R^4 = Me: 12.F12



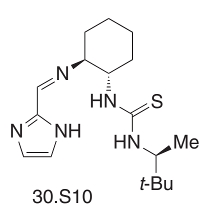
28.F7



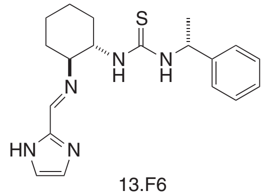
R^1 = Me, R^2 = Me, R^3 = OCO*t*Bu, X = S 12.S3 12.F12 44.F7 30.S7; 112; T5
R^1 = Bn, R^2 = Me, R^3 = *t*Bu, X = S 12.S3 12.F12
R^1 = Bn, R^2 = H, R^3 = OCO*t*Bu, X = O 12.S3 12.F12 30.S7 30.S5; 6; 7
R^1 = Bn, R^2 = Me, R^3 = OCO*t*Bu, X = S 12.S3 12.F12
R^1 = -CH_2-polystyrene, R^2 = H, R^3 = OCO*t*Bu, X = S 12.S3 12.F12



12.F2; 11
30.S4

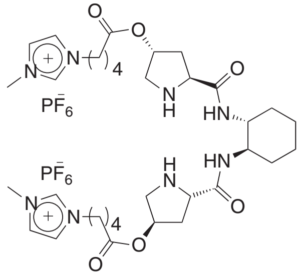


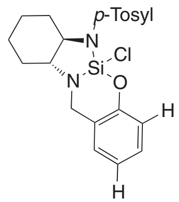
30.S10



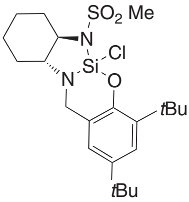
13.F6
13.S11

24.F19

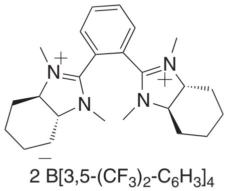




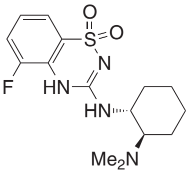
16.S22



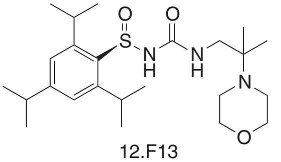
16.S22



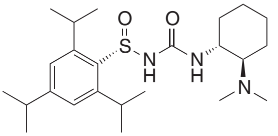
16.S54



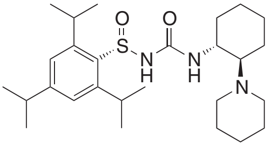
27.S9



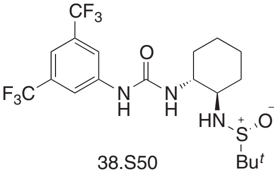
12.F13



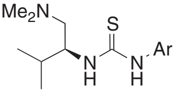
12.F13
34.S13



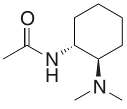
34.S24



38.S50

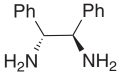


29.S2.5; F2.2

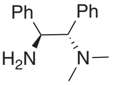


12.F3

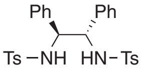
c) Diphenylethylenediamine Derived Catalysts



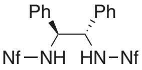
21.S10
21.S31; 24.F33
(21.S10 *ent*)
44.F1



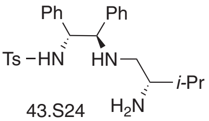
24.S8



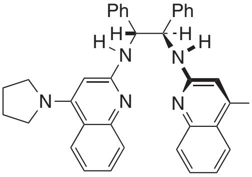
38.S37



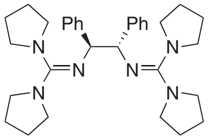
38.S37



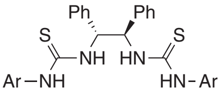
43.S24



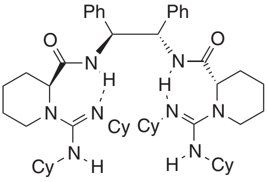
10.S61



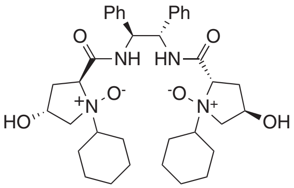
10.S44



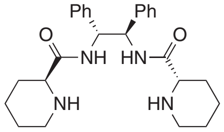
12.F7



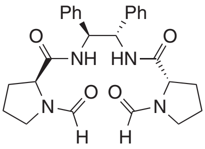
Cy: cyclohexyl
10.S47
38.S33



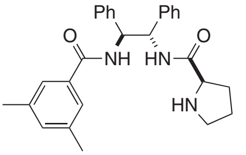
30.T8



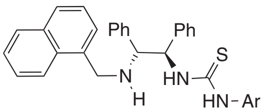
29.S1.9



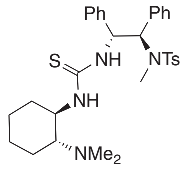
30.S16



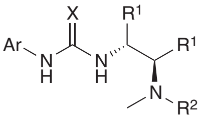
44.F1



29.S2.6; F2.2

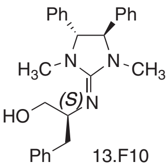


27.S9

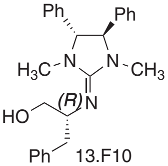


12.F3

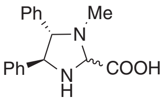
Ar = $3\text{-CF}_3C_6H_4$, n = 2
Ar = $3\text{-CF}_3C_6H_4$, n = 3
X = S, Ar = $3,5\text{-(CF}_3)_2C_6H_3$, R^1 = Ph, Ph, R^2 = Me
X = S, Ar = $3,5\text{-(CF}_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = 3-MeOC_6H_4, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = 3-CNC_6H_4, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = $3\text{-CF}_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = Ph, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = $2\text{-CF}_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = $4\text{-CF}_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
X = S, Ar = $3,5\text{-(CF}_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = ^{i}Pr
X = S, Ar = $3,5\text{-(CF}_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Bn
X = O, Ar = $3,5\text{-(CF}_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Me



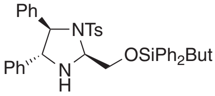
13.F10



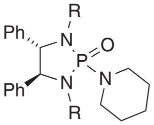
13.F10



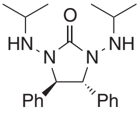
33.S27



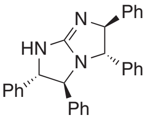
27.F2



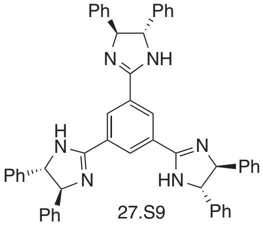
R = Me 15.F4
R = Ph 15.F4



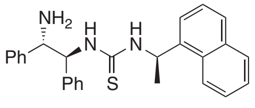
38.S9



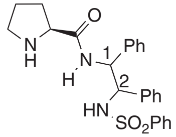
30.S2



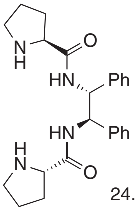
27.S9



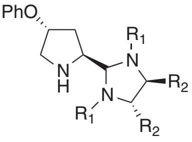
24.F32
34.S2



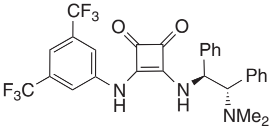
1*R*, 2*R* 25.F13
1*R*, 2*S* 25.F13



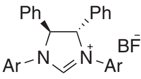
24.F16



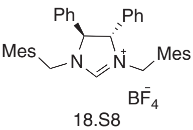
27.F2



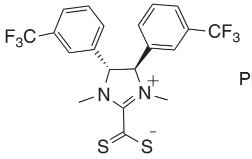
10.S29



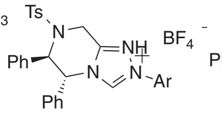
18.S35



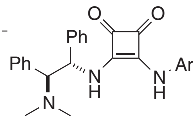
18.S8



36.F5

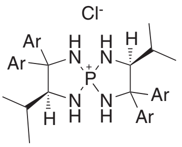


18.S8

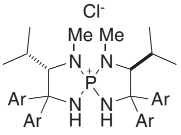


Ar = 3,5-$(CF_3)_2$-C_6H_3
28.T7

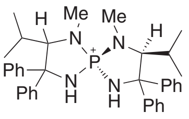
d) Miscellaneous Diamines



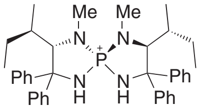
Ar: *p*-CF_3-C_6H_4	10.S65; 28.T8 29.S1.5; T1.1
Ar = 4-Me-C_6H_4	28.T8; 29.S1.5; T1.1
Ar = Ph	29.S1.5; T1.1
Ar = m-Xylyl	29.S1.5; T1.1
Ar: *p*-F-C_6H_4	10.S66



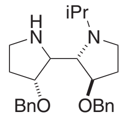
Ar = 4-Cl-C_6H_4-
28.T8



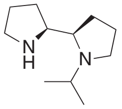
9.F6
10.S67
14.S14
28.S20



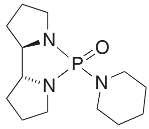
10.S68



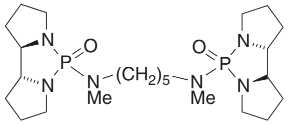
35.S1



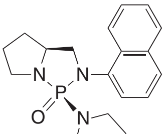
21.S22



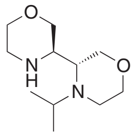
15.F1



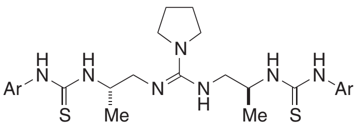
15.F1
15.S7



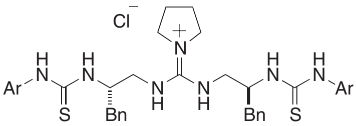
15.F1



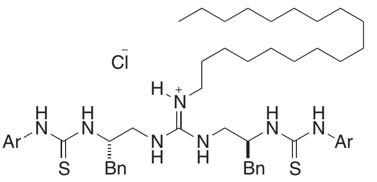
34.S1



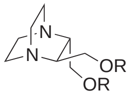
Ar = 3,5-$(CF_3)_2$-C_6H_3-
28.T9



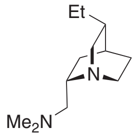
Ar = 3,5-$(CF_3)_2$-C_6H_3-
28.S25
29.S2.14; F2.3



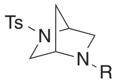
Ar = 3,5-$(CF_3)_2$-C_6H_3-
28.S22; 25
29.S1.2; 1.10



R = Bn	21.S3
R = *t*BuPh_2Si	21.S3
R = 1-naphthyl	21.S3



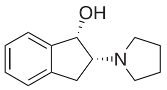
41.S26



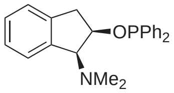
R = $(CH_2)_2NH_2$,	27.S10
R = (CH_2)CH,	27.S10
R = $(CH_2)_3$OH	27.S10

1,2-Aminoalcohols

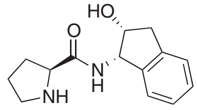
a) Aminoindanols



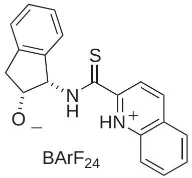
38.S29



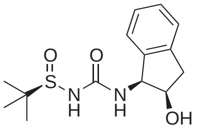
41.S27



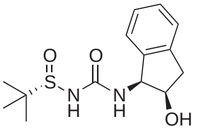
1.S3



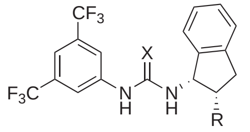
35.S2; 25



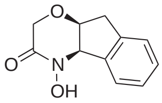
12.F13



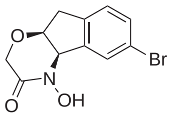
12.F13
29.S2.10; F2.3



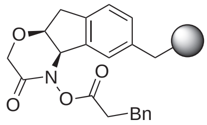
X = O, R = OH 12.F8; 9 ,12.F13 (12.F8; 9 *ent*)
X = S, R = OH 12.F8; 9 35.S2; 35
X = S, R = OSi(CH$_3$)$_3$ 12.F8; 9
X = S, R = H 12.F8; 9



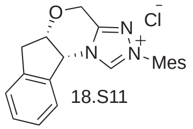
41.F15; S58; 59
43.S13



41.S60

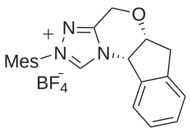


41.S61

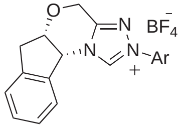


18.S11

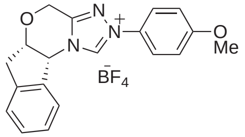
38.39; 40; 42 (18.S11 *ent*)



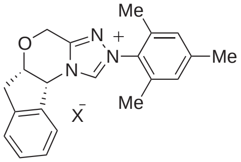
38.S41



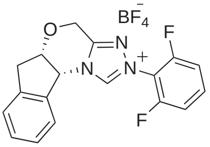
18.S8; 9; 10
Ar = Ph 18.S31 (18.S8 *ent*)
37.F5



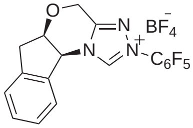
36.S14



X = BF$_4$ 36.S12
X = Cl 40.S40; S41
(40.S40 *ent*)

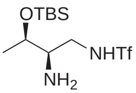


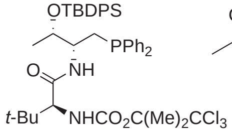
18.S23

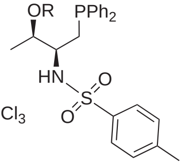


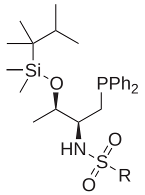
18.S16
18.S24; 25; 27
(18.S16 *ent*)
43.S7; 10 (18.S16 *ent*)

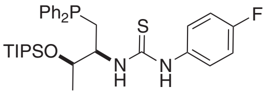
b) Others

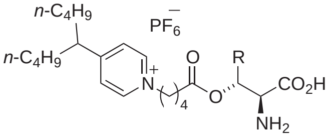

34.S32

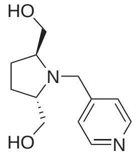

37.F3

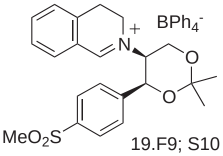

R = TBS 31.F4.2
R = TDS 31.F4.2
R = TBDPS 31.F4.2
R = TIPS 31.F4.2
R = TMS 31.F4.2

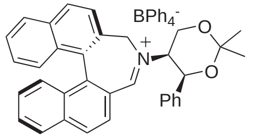

R = 2-naphthyl 31.F4.2
R = 2,4,6-Me-Ph 31.F4.2
R = 4-F-Ph 31.F4.2
R = Me 31.F4.2
R = 4-Me-Ph 31.S4.23

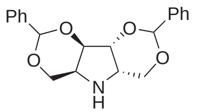

20.S28

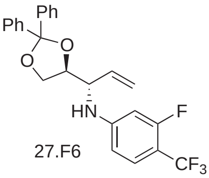

R = H , CH_3 22.S24

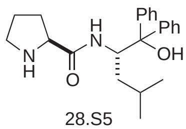

38.S25

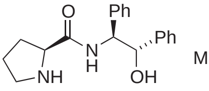

19.F9; S10

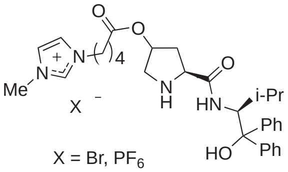

19.F9; S9

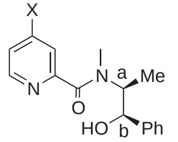

27.F3

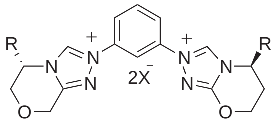

27.F6

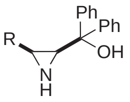

28.S5

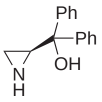

22.S8

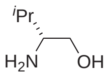

X = Br, PF_6
22.S25

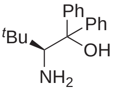

(a*S*,b*R*), X = H 15.F6 32.F3; T1
(a*S*,b*R*), X = Cl 15.F6

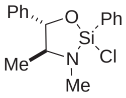

R = Bn; X = Cl^- 18.F3
R = Bn; X = PF^{6-} 18.F3

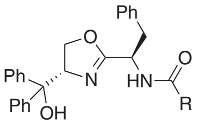

35.S1

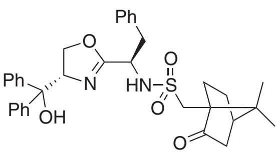

38.S6

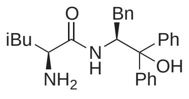

44.F1

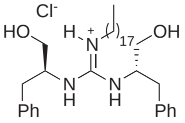

38.S5

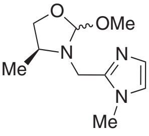

16.S18; 20

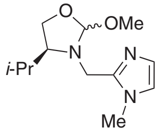

R = CF_3, CCl_3, $CHCl_2$, CH_2F, CH_2Cl
10.S10

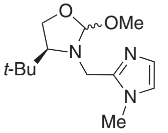

10.S10

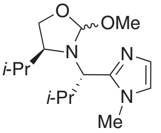

27.S13

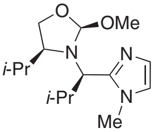

27.S16

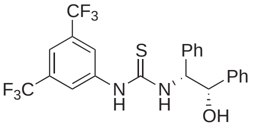

41.F10


41.F10

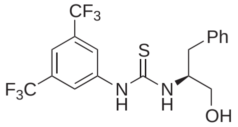

41.F10


41.F10

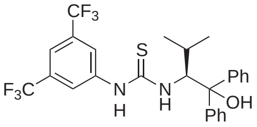

41.F10; S36



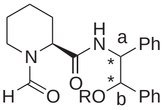
12.F8



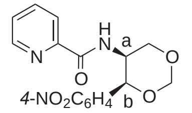
12.F8



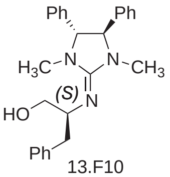
21.S9



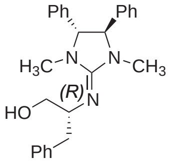
(aS,bS), R = Ac	15.F5
(aS,bR), R = Ac	15.F5
(aS,bR), R = MOM	15.F5; S28
aS,bR), R = Me	15.F5



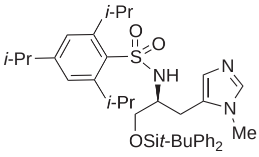
15.F6



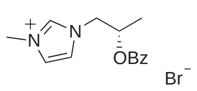
13.F10



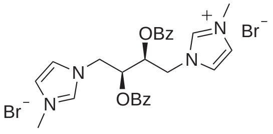
13.F10



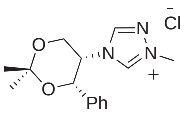
41.S23



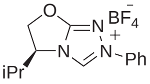
16.S55; 57



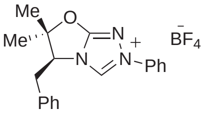
16.S26; 57



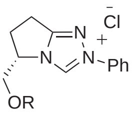
18.F3



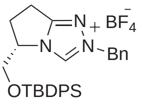
18.F3



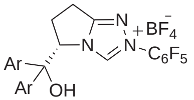
40.S21



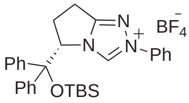
R = Me 18.F3
R = Ph 18.F3



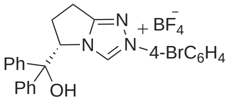
18.S11; 12



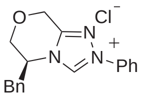
18.S3; S6
Ar = Ph 18.F3



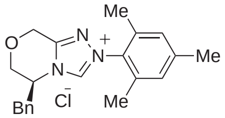
18.S31; 32
37.S12



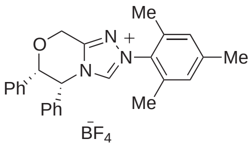
18.S4



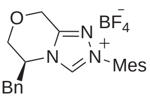
18.F3



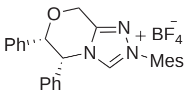
36.S18



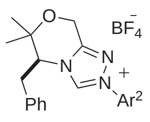
36.S17



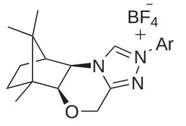
18.S11; 13



18.S21; 26

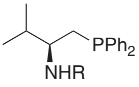


Ar^2 = 2,4,6-Me_3-C_6H_2-
28.S28

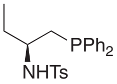


18.S8; 28

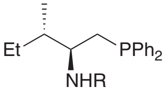
1,2-Aminophosphines



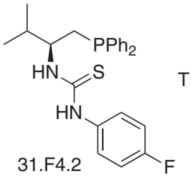
R = Boc: 31.F4.2
R = Ac: 31.F4.2
R = Ts: 31.F4.2



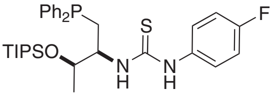
31.F4.2



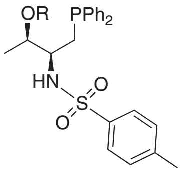
R = 3,5-$(CF_3)_2C_6H_3CO$
37.F3



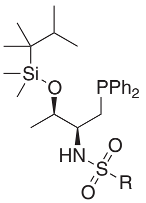
31.F4.2



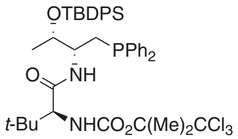
20.S28



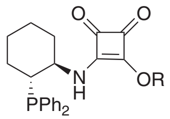
R = TBS 31.F4.2
R = TDS 31.F4.2
R = TBDPS 31.F4.2
R = TIPS 31.F4.2
R = TMS 31.F4.2



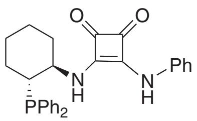
R = 2-naphthyl 31.F4.2
R = 2,4,6-Me-Ph 31.F4.2
R = 4-F-Ph 31.F4.2
R = Me 31.F4.2
R = 4-Me-Ph 31.S4.23



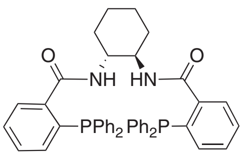
37.F3



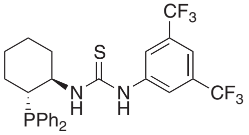
R = Et 10.S28 31.S4.22
R = i-Pr 31.S4.22
R = Bn 31.S4.22



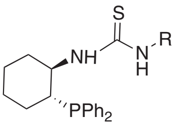
31.S4.22



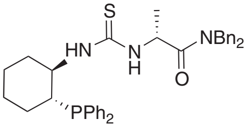
41.S45



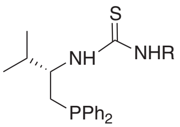
31.S4.22



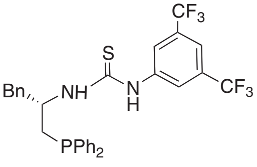
R = c-C_6H_{11} 31.S4_25
R = C_6H_5 31.S4_25; 4_29
R = 3,5-$(CF_3)_2C_6H_3$ 31.S4_25; 4_27
R = n-C_4H_9 31.S4_25
R = n-$C_{12}H_{25}$ 31.S4_25
R = n-$C_{18}H_{37}$ 31.S4_25
R = $C_6H_5CH_2$ 31.S4_25



37.F3

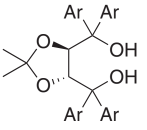


R = C_6H_5 31.S4_25
R = 4-$MeOC_6H_4$ 31.S4_25
R = 4-ClC_6H_4 31.S4_25
R = 3,5-$(CF_3)_2C_6H_3$ 31.S4_25
R = *c*-C_6H_{11} 31.S4_25
R = *n*-C_8H_{17} 31.S4_25



31.S4_28

TADDOL-Derived Catalysts

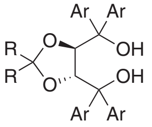


Ar = 1-naphthyl

10.S1; 2; 4; 5; 7

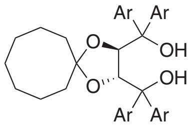
28.F7; S10

38.S17; 34; 35



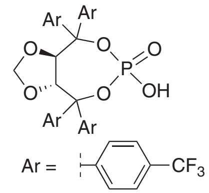
Ar = 1-naphthyl
R = -(C_5H_{10})-

10.S3

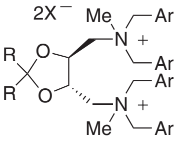


Ar = pyren-1-yl

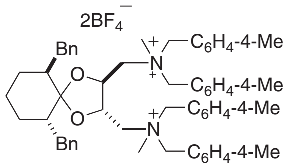
10.S11



11.S5

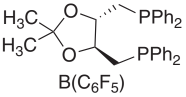


14.S10



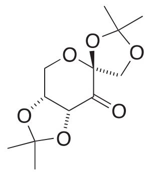
28.S24

44.F11

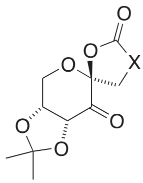


31.F7

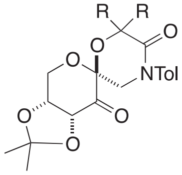
Carbohydrate-Derived Catalysts



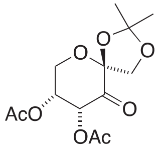
19.F1; S2; 3; 4
27.F3



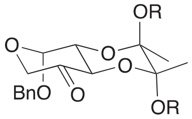
X = NBoc 19.F5; S5; 20
X = NTol 19.F5; S7; 8
X = N(4-EtC_6H_4) 19.F5



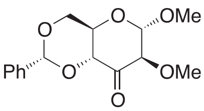
R = H 19.F6; S6
R = Me 19.F6



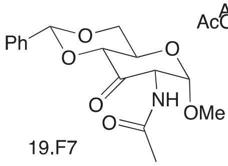
19.F8



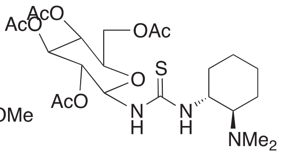
R = ^{i}Bu 19.F7
R = Me 19.F7



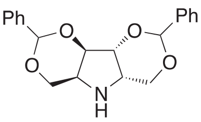
19.F7



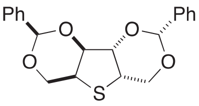
19.F7



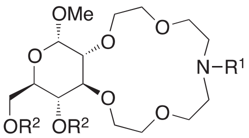
29.F2.2



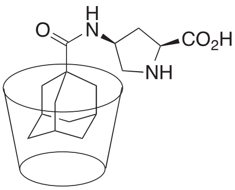
27.F3



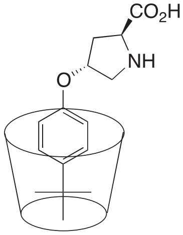
20.F3; S5



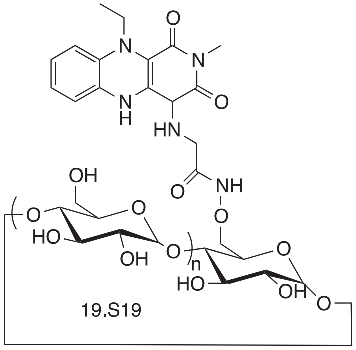
27.S15



24.F12

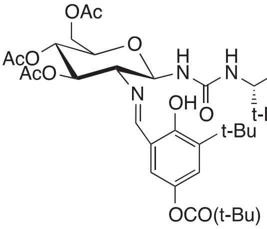


sulfated β-CD
24.F12

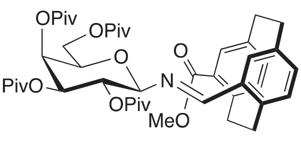


19.S19

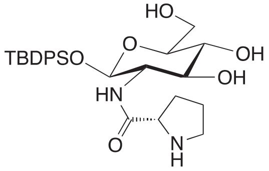
n = 5



30.S11

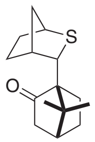


30.T13

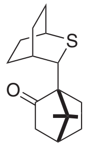


24 F17

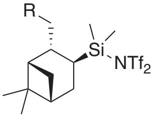
Terpene-Derived Catalysts



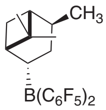
16.S25
20.T3



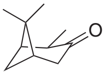
20.T3



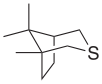
16.S7; 8



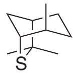
31.F7



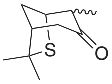
19 F1



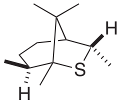
20.S10



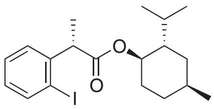
isothiocineole
20.S9



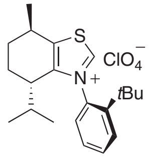
20.S5



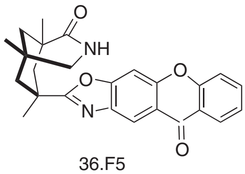
20.S5; T1



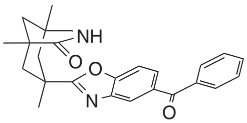
19.S17



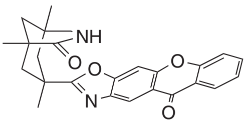
18.F3



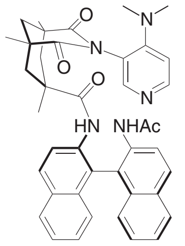
36.F5



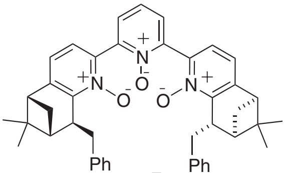
38.S22



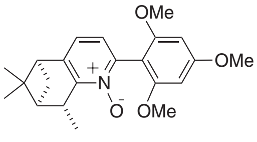
38.S22



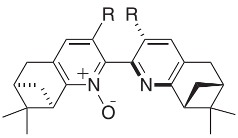
41.F1



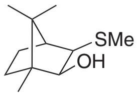
15.F2



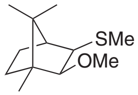
15.F2; S4; S7



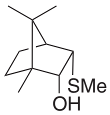
R = H 15.F2; 8
R = Me 15.F2; S4



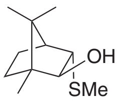
20.2a; S19



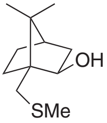
20.2b



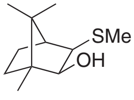
20.2c



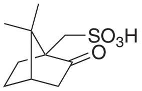
20.2d



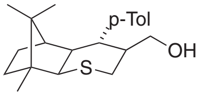
20.S3; 5



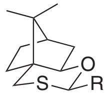
20.S5



43.S21

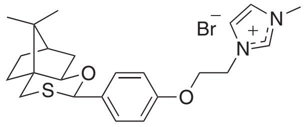


20.S5; 17

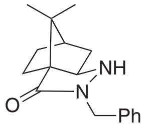


20.T1; T2

R = Me 20.T3; S18

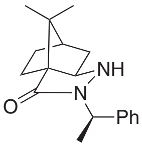


22.S36

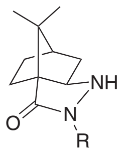


24.F39

38.S2

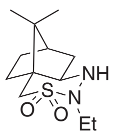


24.F39



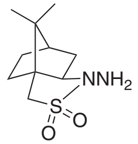
R = Bn or CH_2-1-Naph

37.F1

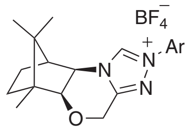


24.F39

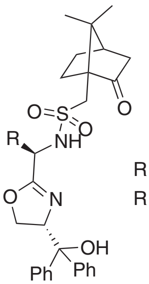
38.S2



38.S19

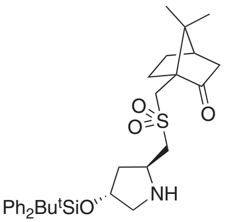


18.F3

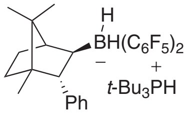


R = Bn: 10.S10

R = iPr: 38.S36

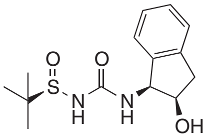


27.F2

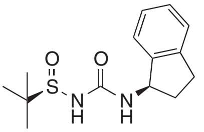


31.F7; S32

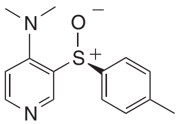
Chiral Sulfoxides



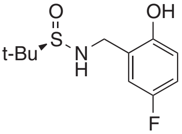
12.F13
29.S2.10; F2.3



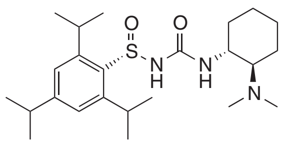
12.F13



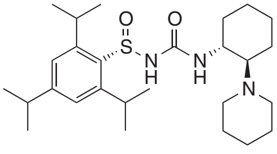
41.F1



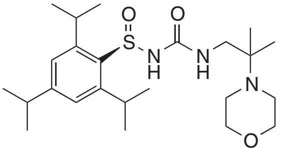
15.F5
31.F3; T1



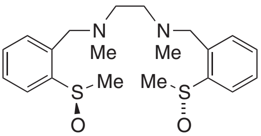
12.F13
33 S13



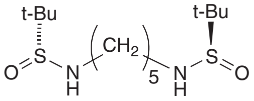
34.S24



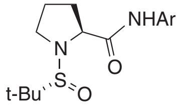
12.F13
34.S25



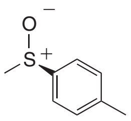
15.F3



15.F5
31.F3; T1



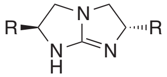
Ar = 3,5-$Me_2C_6H_3$: 15.F5
31.F3; T1
Ar = 3,5-$iPr_2C_6H_3$: 31.F3; T1; S23
Ar = 2,6-$iPr_2C_6H_3$: 15.F5



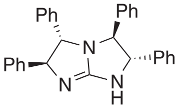
15 S10

Miscellaneous

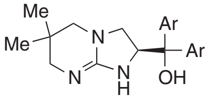
a) Cyclic Guanidines



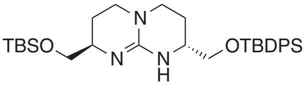
R = Ph 10.S43 13.F9 31.S13
R = iPr 13.F9
R = tBu 10.S43 13.F9; S15
27.S5 34.S19 40.S29
R = Bn 13.S16 38.S26



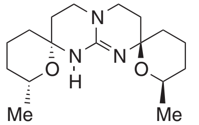
30.S2



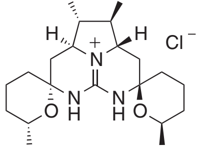
Ar = 3,5-$(CF_3)_2$-C_6H_3
10.S56
28 S18



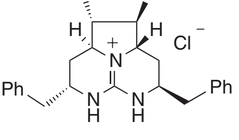
16.S1
10.S42



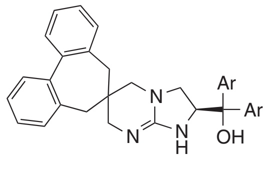
10.S42



14.S4

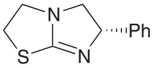


27.S16



Ar = 3,5-$(CF_3)_2$-C_6H_3

b) Tetramisol Analogs



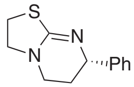
(-)-Tetramisole

31 .S4.11

36.S20

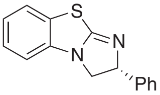
40.S16

41.F3



Homotetramisole

41.F3

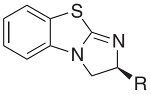


BTM

41.F1; 3; 4; 13;

S2; 3; 4; 5; 6;

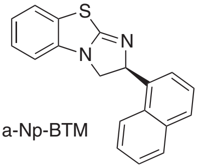
7; 8; 10; 11; 46



iPr-BTM R = iPr 41.F4; T1

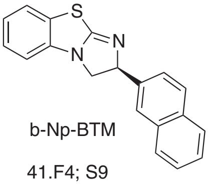
tBu-BTM R = tBu 41.F4

Bn-BTM R = Bn 41.F4



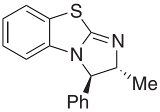
a-Np-BTM

41.F4



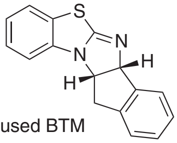
b-Np-BTM

41.F4; S9



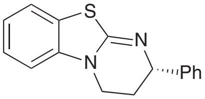
t-Bu-BTM

41.F4



fused BTM

41.F4



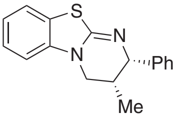
(-)-HBTM, 94

31 .S4.11

40.S17

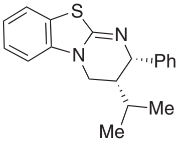
41.F3; S5

41.F13

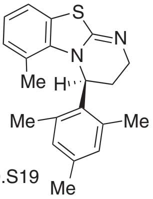


Me-HBTM R = Me 41.F3; S5

iPr-HBTM R = iPr 41.S12



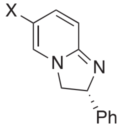
40.S17; 18



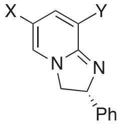
40.S19

c) Imidazolines

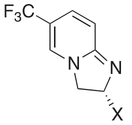
PIP analogs



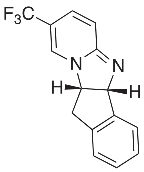
X-PIP
X = CF_3 41.F2; 3; 13
X = Br 41.F1; 2
X = H 41.F2
X = NO_2 41.F2
X = Bn 41.F1



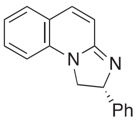
X-PIP analogs
X = $CONEt_2$, Y = H 41.F2
X = CN, Y = H 41.F2
X = H, Y = F 41.F2
X = Br, Y = Br 41.F2



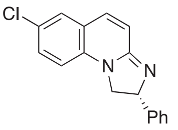
CF_3-PIP analogs
X = i-Pr 41.F3
X = t-Bu 41.F3



CF_3-PIP analog
41.F3

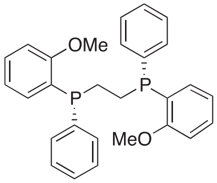


DHIQ
41.F3

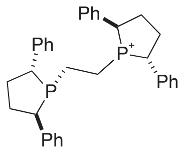


Cl-PIQ
41.F1; 2; 13; S2; 3; 4; 5; 47

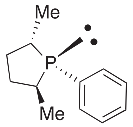
d) Chiral Phosphines



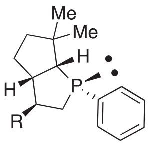
(*R,R*)-DIPAMP
37.F3



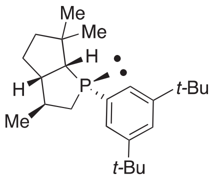
20.F5; S28



41.F1

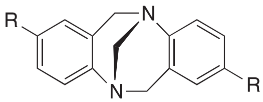


R = H: 41.F1
R = Me: 41.F1



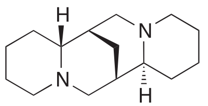
40.S10
41.F1

e) Molecular Tweezers

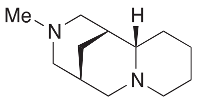


R = Me: (+)-Tröger's base 27.S2
37.F6

R = H: 31.S4.12

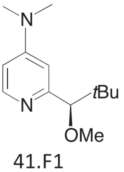


31.S4.12

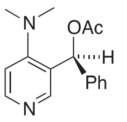


31.S4.12

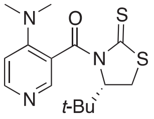
f) Unclassed Catalysts



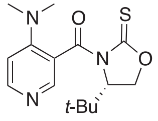
41.F1



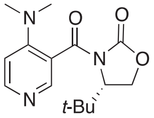
41.F1



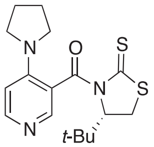
41.F1; 6; T1; S15; 16



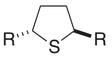
41.F6



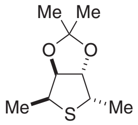
41.F6; T1



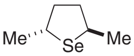
41.F6; T1



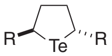
R = Me 20.F1; 2; 3; 4; S5; 7
R = Et 20.S5; 7
R = iPr 20.S13
R = tBu 20.S13



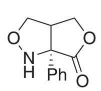
20.F3; S5



20.S32

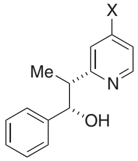


R = Et: 20.S34
R = Me: 20.S33

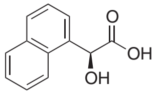


$HClO_4$

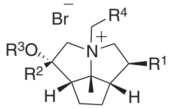
38.S6



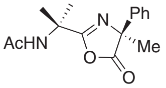
X=H 42.F5; S38
X=Cl 42.F5; S38



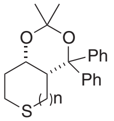
10.S7
16 S51, 51



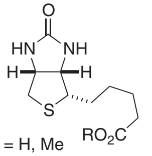
14 S4



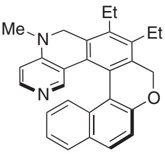
41.F11



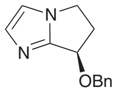
n = 0, 1
20.S5



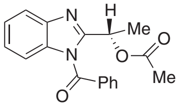
R = H, Me
20.S5



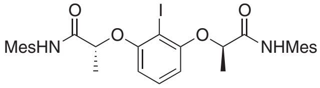
41.S18



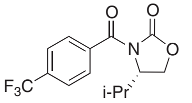
40.S20



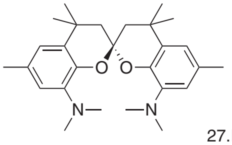
41.F11



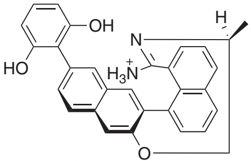
19 F11; S16



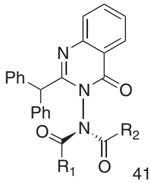
41.F11



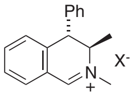
27.F5



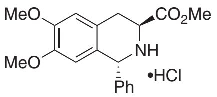
38.S20 TFPB



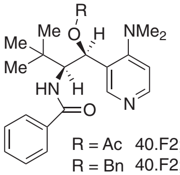
41.F11



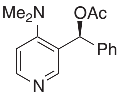
19.F9



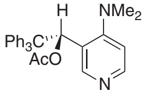
38.S6



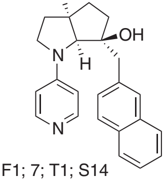
R = Ac 40.F2; S14
R = Bn 40.F2; S15



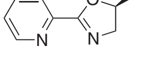
40.S9



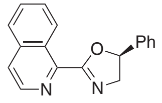
40.S10; 11; 12; 13



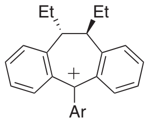
41.F1; 7; T1; S14



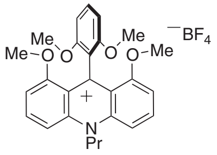
R = Ph 15.F6
R = *t*-Bu 15.F6



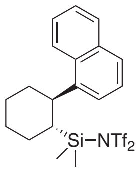
15.F6
32.F3; T1



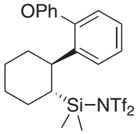
16.S41; 42; 43 (X = $^{-}ClO_4$)
Ar = Ph= 16.S48 (X = $^{-}PF_6$)



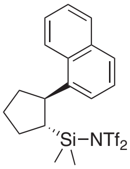
16.S49



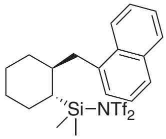
16 S9



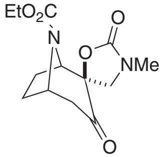
16 S9



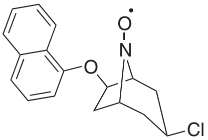
16 S9



16 S9



19.F7; 9



19 F14
44: S22

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